MEDICAL LIBRARY
HISTORICAL BUILDING
DES MOINES, IOWA

JAN 25 1949

Cleveland Clinic Quarterly

JAN 25 1949

A Bulletin Published by

MEDICAL LIBRARY
HISTORICAL BUILDING
DES MOINES, IOWA

The Staff of the Cleveland Clinic

CLEVELAND, OHIO

Vol. 16 JANUARY, 1949 No. 1

CONTENTS

Radioactive Iodine in the Treatment of Hyperthyroidism
George Crile, Jr., M.D., E. Perry McCullagh, M.D., and Otto Glasser, Ph.D. 1

Diagnosis and Treatment of Macrocytosis
Donald W. Bortz, M.D., and Russell L. Haden, M.D. 8

Bronchial Adenoma
Donald B. Effler, M.D. 12

Double Ventricular Shift in a Case of Cerebral Hemiatrophy
Robert M. Geist, Jr., M.D., and C. Robert Hughes, M.D. 17

The Use of Sex Hormones in Cancer
E. Perry McCullagh, M.D. 21

Thrombophlebitis
Fay LeFevre, M.D. 33

Reimplantation of the Ureter into the Bladder
J. G. Warden, M.D., and C. C. Higgins, M.D. 38

Mesenteric Cyst With Intestinal Obstruction
Arthur G. Michels, M.D., and Thomas E. Jones, M.D. 47

Idiopathic Steatorrhea
Charles H. Brown, M.D. 52

Announcements 59

The Frank E. Bunts Educational Institute—Diabetes 60

Issued in four numbers during the year, one in January and one in April, one in July and one in October, by The Cleveland Clinic Foundation, 2020 East 93rd Street, Cleveland 6, Ohio.

Entered as second-class matter March 4, 1935, at the Post Office at Cleveland, Ohio, under the act of August 24, 1912.

Copyright, 1949, by The Cleveland Clinic Foundation.

Cleveland Clinic Quarterly

EDIC
2.85 P
May 12, 1932 Hartzbarg Craftsmen - Binding

EDICAL LIBRARY
CRICAL BUILDING
NES, IOWA

JAN 25 1949

EXPERIENCE WITH RADIOACTIVE IODINE IN THE TREATMENT OF HYPERTHYROIDISM

GEORGE CRILE, JR., M.D., Department of General Surgery,
E. PERRY McCULLAGH, M.D., Department of Endocrinology
and
OTTO GLASSER, Ph.D., Research Division

History

THE use of radioactive iodine in the treatment of hyperthyroidism was initiated seven years ago by Hertz and Roberts[1] in Boston and Hamilton and Soley[2] in San Francisco. The iodine was made in cyclotrons and was not available for general use. Two years ago, however, the Atomic Energy Commission released I^{131}, prepared in the atomic pile at Oak Ridge, to any institution with a committee composed of a qualified radiologist, surgeon, and internist. Since then radioactive iodine has been used extensively throughout the country in the treatment of hyperthyroidism. This paper is a report of the results obtained at the Cleveland Clinic in the treatment of 105 patients with hyperthyroidism.

The Nature of I^{131}

I^{131} differs from many radioactive substances in that its half life, or the length of time it takes to expend one half of its potential radioactivity, is only eight days. At the end of a month most of the radioactivity is gone, and by two or three months practically none remains. Since the radioactivity of I^{131} disappears in a short time there is no danger of later ill effects due to retention of a long-lived radioactive substance in the body.

A second characteristic of I^{131} which increases the safety of its use in the treatment of hyperthyroidism is the fact that its radiation is largely in the form of beta rays. These rays do not penetrate the tissues for more than 1 or 2 mm., about the thickness of a thumbnail. Since the radioactive material is concentrated in the thyroid and the beta rays do not penetrate far enough to damage tissues outside of the thyroid, no demonstrable damage is done to tissues outside of the thyroid gland. Even when doses totaling 100 times as much as the average therapeutic dose are given no changes are demonstrable, either histologically or functionally, in the kidneys, bone marrow, testes, or other organs.[3] Neither tetany nor damage to the recurrent laryngeal nerves has been observed following its use. Thus I^{131}, given in average doses, does not induce any immediate reaction other than destruction of functioning thyroid tissue.

A third property that makes I^{131} well adapted to treating hyperthyroidism is the fact that the chemical and physiologic behavior of the radioactive element is exactly the same as that of ordinary iodine. Therefore the normal thyroid

gland takes up and stores I^{131} the same way it takes up stable iodine and in hyperthyroidism the overactive thyroid takes it up even more rapidly and concentrates it in even greater amounts. Thus it is estimated that in patients with hyperthyroidism I^{131} is concentrated in the thyroid in amounts 10,000 times greater than in the blood or in any other organ.[4] Each gram of thyroid tissue contains 10,000 times as much I^{131} as does a gram of any other tissue in the body and consequently receives a proportional intensity of radiation. The I^{131} is stored in the thyroid until it has lost the major part of its radioactivity after which most of it is excreted by the kidneys as ordinary (nonradioactive) iodine.

Hyperthyroidism is caused by hypersecretion of the iodine-containing hormone thyroxine. The thyroid epithelial cells pick up iodine from the blood and convert it into thyroxine. If the iodine that these cells take up is radioactive, the cells are selectively inactivated or destroyed by the radiation. I^{131} is concentrated in those parts of the thyroid that are functioning most actively. In hyperthyroidism the parts of the gland that are responsible for the hyperthyroidism take up and store I^{131} and are inactivated or destroyed, whereas any inactive parts of the thyroid take up virtually no I^{131} and are spared. In short radioactive iodine selectively inactivates those cells of the thyroid that are overactive and spares those that are not functioning. Theoretically, therefore it should be possible to control hyperthyroidism in all cases if adequate amounts of I^{131} are given.

The amount of irradiation that is received by the thyroid after an average dose of radioactive iodine is much greater than the amount of irradiation that can be given by roentgen therapy without damage to the skin. An average dose of 4 mc.* of I^{131}, given to a patient with Graves' disease and a goiter estimated to weigh 50 Gm. which takes up 50 per cent of the administered dose, delivers the equivalent of 4000 r to the thyroid.

Although there is little experimental and no clinical evidence to suggest that intensive irradiation of this nature will be carcinogenic, the possibility warrants consideration. We believe it unlikely that the incidence of carcinoma of the thyroid will be significantly altered by treatment with radioactive iodine. In patients treated as long as seven years ago carcinomas have not developed and there is no clinical or experimental evidence that they will develop (Hertz and Roberts[1]). It is therefore safe to prescribe I^{131} for older patients with hyperthyroidism or for patients with short life expectancies.

Although we also believe that it is safe to treat younger patients with I^{131} we are unable to prove its ultimate safety nor will anyone be in a position to do so for fifty years. For this reason the arguments of those who foresee trouble cannot be refuted. One can only point out that the same reasoning applies to any new therapeutic agent, the ultimate effects of which cannot be forecast. In the unlikely event that patients treated with I^{131} should show a tendency to develop carcinoma of the thyroid, prophylactic thyroidectomy still would be a practical method of avoiding this complication.

**Oak Ridge standard.*

Technic of Treatment

I^{131} is flown from Oak Ridge once every two weeks. It is measured and divided into doses of 2, 4, 6, and 8 mc. The I^{131} is in the form of sodium iodide and is dissolved in water. It is colorless and tasteless. The amount of I^{131} contained in the average therapeutic dose is equivalent to the iodine in 1/50,000 of a drop of Lugol's solution.

From the patient's standpoint, treatment consists in merely drinking a third of a glass of what appears to be plain water. From two to four hours later the radiation over the thyroid is measured with a Geiger counter so that an estimate can be made of the amount of I^{131} the thyroid has picked up and of the amount of radiation it will receive. The patient then returns home. There is no reaction except in cases where very large doses are given as in the treatment of cancer of the thyroid. Neither radiation sickness nor irritation of the thyroid area is observed after the ordinary dose.

Further medical observation is not required for two months. At this time the basal metabolism is rechecked and the patient is either released with the hyperthyroidism controlled or is given a second dose. About half of the patients with Graves' disease become symptom free after a single treatment and most of the remainder following a second. Patients with large adenomatous goiters may require three or four treatments before the hyperthyroidism is completely controlled.

From the physician's standpoint the problem of measuring the dose and protecting the person handling the I^{131} is more complicated. These aspects of treatment should be delegated to qualified radiologists.

Dosages*

The initial dose of I^{131} for patients with Graves' disease is one-half to two-thirds of the average dose required to effect a cure. If 4 mc. are given about half of the patients are well after a single treatment and only 10 per cent develop even a transitory hypothyroidism.

The dose employed in the second treatment depends on the response of the hyperthyroidism to the first treatment. If the basal metabolic rate is unchanged two months after the first treatment, the dose for the second treatment may be double the first. If the basal metabolic rate has fallen half way to normal the first dose is repeated. If the basal metabolic rate has dropped two-thirds of the way to normal, half of the original dose is given. But if there is only slight residual hyperthyroidism, or if the basal metabolic rate is at the upper limit of normal, no further treatment is given, because maximum effects of a single dose sometimes are not apparent for three or four months.

In Graves' disease the average initial dose is 4 mc. unless the thyroid is unusually large and the hyperthyroidism severe in which case 6 or even 8 mc. may be given. Our experience has indicated that the dose required to control

**Oak Ridge standard.*

the hyperthyroidism of Graves' disease is dependent more upon the severity of the hyperthyroidism than upon the size of the gland. If the hyperthyroidism is severe it will be necessary to inactivate the thyroid more completely and larger doses of I^{131} are required. If the hyperthyroidism is mild, a smaller dose will suffice to reduce the excessive secretion of thyroid hormone to normal.

In nodular goiter with hyperthyroidism the average initial dose is 8 to 15 mg., depending on the size of the gland. Since the take-up of iodine in nodular goiters is irregular many areas do not receive significant amounts of radiation. It is therefore difficult to induce hypothyroidism in patients with nodular goiters and it is difficult to control the hyperthyroidism except by giving large doses and repeating them several times. As the most active areas are inactivated the less active ones begin to function. When treatment is repeated these new areas absorb I^{131} and in turn are inactivated. Thus the thyroid is inactivated area by area, until normal function is restored.

Rationale of Treatment with I^{131}

It requires about 30 mc. of I^{131} to induce myxedema in a patient with a normal thyroid, yet 3 or 4 mc. may induce hypothyroidism in a patient with Graves' disease. This observation parallels our experience in the surgical treatment of hyperthyroidism. A partial thyroidectomy for Graves' disease in which 5 Gm. or more of thyroid is left, often is followed by myxedema, whereas even the most radical subtotal thyroidectomy performed upon patients with normal thyroids or with nodular goiters causes no more than a transitory lowering of the basal metabolic rate. Hence there must be factors other than the amount of thyroid tissue remaining after either thyroidectomy or irradiation that influence the development of hypothyroidism.

Patients with Graves' disease, even without treatment, occasionally will enter a remission and may even develop hypothyroidism. Such cycles of thyroid activity are not so much dependent upon the amount of thyroid tissue present as they are upon the activity of that tissue. In Graves' disease the functional activity of the thyroid is dependent primarily upon the unknown factors that cause the underlying disorder.

We do not therefore believe it is possible to cure Graves' disease either by irradiation or by thyroidectomy without occasionally causing hypothyroidism. Any therapeutic measure which interrupts the vicious circle of thyroid stimulation responsible for the development and maintenance of Graves' disease may effect so complete a suppression of thyroid stimulation that the thyroid remnants will not function. If the hyperthyroidism is controlled no one can predict in any single cases whether the thyroid will function normally, whether hyperthyroidism will later recur, or whether hypothyroidism will develop.

These considerations suggest that the treatment of hyperthyroidism with I^{131} is as empiric as thyroidectomy. Regardless of the care that is exerted in attempting to standardize the amounts of radiation given to each gram of thyroid tissue, in some cases hypothyroidism will occur while other patients will prove refractory to the ordinary doses and will require more than the

average amount of irradiation. Therefore we believe that the best way to estimate the proper total dose is by observation of the physiologic response to a small initial dose. The incidence of hypothyroidism has been lower following this method of treatment than when the estimated full therapeutic dose was given.

Advantages of Treatment with I^{131}

The cost of controlling hyperthyroidism with I^{131} is much less than that incurred by the average patient for professional and hospital services incident to a thyroidectomy and is less than that of a year's treatment with an antithyroid drug.

Hospitalization, loss of work, and the inconvenience involved in repeated visits to the physician are avoided. There is no mortality, no morbidity and no discomfort following its use. We have not yet seen recurrences of hyperthyroidism. The incidence of hypothyroidism so far has been about the same as that following an adequate thyroidectomy—9.5 per cent for patients with Graves' disease and none for those with nodular goiter with hyperthyroidism.

Results of Treatment with I^{131}

In the past year 105 patients with hyperthyroidism have been treated at the Cleveland Clinic with I^{131}. Only 34 patients have been treated long enough to allow three months' observation. Since it takes two to four months for the full effect of treatment to become apparent, the more recent cases are not included in the summary of results. Two elderly patients died within two months after treatment, 1 of a cerebral hemorrhage and 1 of an acute pulmonary disease unrelated to the treatment. One patient decided two weeks after the first treatment to be operated upon elsewhere and did not return for observation. All other patients have been followed from three to ten months.

Results of Treatment of Graves' Disease

In 19 of the 21 patients with Graves' disease the hyperthyroidism has been completely controlled and the goiters have disappeared.

1. The average basal metabolic rate has fallen from +45 per cent before treatment to 0 per cent.
2. Control of the hyperthyroidism was effected by 1 treatment in 12 cases, by 2 treatments in 6, and by 3 treatments in 1.
3. The hyperthyroidism was well controlled in an average of three months after the first treatment.
4. The average total dose was 6.7 mc.
5. The average size of the thyroids has decreased from an estimated weight of 61 Gm. to 27 Gm.

One patient is improved three months after a single treatment, and has received a second.

The last patient of the group has received 9 mc. in 2 treatments and is no better. In this case the hyperthyroidism is atypical and the hypermetabolism does not appear to be caused by overactivity of the thyroid gland. Two thyroidectomies performed elsewhere did not control the patient's symptoms, no thyroid is palpable, the thyroid takes up only 25 per cent of the administered I^{131}, and sections of the thyroid removed previously showed no hyperplasia.

Results of Treatment of Nodular Goiter with Hyperthyroidism

In 5 of the 10 patients with nodular goiters the hyperthyroidism has been controlled and the goiters are smaller.

1. The average basal metabolic rate has fallen from +39 to +6 per cent.
2. Control of the hyperthyroidism was effected by 2 treatments in 3 cases and by 3 treatments in 2.
3. The hyperthyroidism was well controlled in an average of five months after the first treatment.
4. The average total dose was 15.4 mc.
5. The average size of the thyroid has decreased from an estimated weight of 123 Gm. to 70 Gm.

Four patients are improved and are still under treatment.

One patient shows no improvement after 1 treatment and is still under treatment.

The patients whose hyperthyroidism has been controlled by treatment with I^{131} appear to be as well as those whose hyperthyroidism has been controlled by thyroidectomy. The diffuse goiters of Graves' disease disappear and are no longer palpable. Nodular goiters usually shrink, but do not disappear. When the hyperthyroidism is controlled auricular fibrillation tends to revert to normal rhythm just as after thyroidectomy.

There has been no radiation sickness and no exacerbation of the hyperthyroidism. No symptoms of local irritation have been observed. There has been no tetany, no change in levels of blood calcium, no change in menstruation, no depression of hematopoiesis, and no alteration in renal function. One patient with a nodular goiter and moderate hyperthyroidism had had one kidney removed and had a hydronephrosis of the other. The level of blood urea was 80 mg. per cent before treatment. Following administration of 11 mc. of I^{131} the hyperthyroidism was controlled and there was no change in renal function or retention of nitrogen.

Two patients with Graves' disease developed hypothyroidism four months after treatment with 8 mc. and 3 mc. of I^{131} respectively. One of these patients already appears to be recovering. In the majority of cases of hypothyroidism that have been reported following treatment with I^{131} the patients have made a spontaneous recovery.[5]

Summary

1. During the past year 105 patients with hyperthyroidism have been treated with I^{131}.

2. Radioactive iodine is a simple, effective, and apparently a safe method of treating patients with hyperthyroidism.

3. Neither hospitalization nor supervision of the patient is required and the cost of treatment is less than that of thyroidectomy or prolonged medical treatment.

4. In 90 per cent of the cases of Graves' disease hyperthyroidism is controlled in two to four months by 1 or 2 treatments. Ten per cent of the patients may require a third treatment.

5. Diffuse goiters disappear after treatment and the symptoms of hyperthyroidism are as completely and effectively controlled as by an adequate thyroidectomy.

6. The only complication which has occurred following treatment with I^{131} is hypothyroidism, usually transitory, which occurs in about the same proportion of cases as after thyroidectomy.

7. Hyperthyroidism associated with nodular goiters is more difficult to control than the hyperthyroidism of Graves' disease, requires larger doses of I^{131} and more treatments.

8. Although nodular goiters become smaller after treatment with I^{131} they do not disappear.

9. I^{131} is the preferred treatment for elderly patients with hyperthyroidism, for those who are poor surgical risks, and for those with recurrent hyperthyroidism.

10. I^{131} appears to be an acceptable method of treatment for younger patients with Graves' disease but final evaluation of its safety in young patients will require many years of observation. At the present time we are employing it in selected cases.

11. I^{131} is not recommended in the treatment of hyperthyroidism occurring in young patients with nodular goiters.

References

1. Hertz, S., and Roberts, A.: Radioactive iodine in study of thyroid physiology. J.A.M.A. **131**:81-86 (May 11) 1946.
2. Hamilton, J. G., and Soley, M. H.: Studies in iodine metabolism of thyroid gland in situ by use of radio-iodine in normal subjects and in patients with various types of goiter. Am. J. Physiol. **131**:135-143 (Nov.) 1940.
3. Hertz, S.: Personal communication.
4. Hamilton, J. G.: Use of radioactive tracers in biology and medicine. Radiology **39**:541-572 (Nov.) 1942.
5. Werner, S. C., Quimby, E. H., and Schmidt, C.: Clinical use of radioactive iodine. Bull. New York Acad. Med. **24**:549-560 (Sept.) 1948.

DIAGNOSIS AND TREATMENT OF MACROCYTOSIS

DONALD W. BORTZ, M.D., and RUSSELL L. HADEN, M.D.

Department of Internal Medicine

MACROCYTOSIS is present in any condition in which there is an outpouring of immature red blood cells or in which there may be faulty absorption, utilization, or storage of the erythrocyte-maturing factor (E.M.F.). It may be suspected on routine examination of the stained blood smear, but an accurate diagnosis must await the actual measurement of the mean cell diameter by means of an erythrocytometer or the calculation of the volume index. The volume index is determined by dividing the per cent normal red blood count into the per cent normal hematocrit reading. A volume index of 1.08 or above indicates macrocytosis.

With any sudden demand upon the hematopoietic system precipitated by an acute loss of blood, the bone marrow endeavors to compensate by releasing immature red blood cells, or reticulocytes, which are larger than mature erythrocytes. This results in reticulocytosis, which may at times reach levels as high as 45 or 50 per cent.

An example of this condition was found in a 24-year-old girl with portal hypertension. During the preceding ten years she had had repeated episodes of hematemesis, for which 81 transfusions had been given. Two years after the onset of bleeding a splenectomy had been performed at another institution, and this was followed by multiple injections of esophageal varices. During the course of several hospitalizations a devascularization of the stomach and several esophagoscopies were carried out in an effort to control bleeding points. She had recently been hospitalized for a recurrence of severe hematemesis, at which time her blood count had reached 2,970,000 red cells, hemoglobin 49 per cent, volume index 1.28, color index 0.83, and a reticulocyte count of 20.5 per cent. Examination of the bone marrow at this time revealed an extremely erythroblastic marrow.

In this case, in an effort to compensate for repeated and massive blood loss, the bone marrow had released many cells which were not completely matured, producing reticulocytosis and resulting in macrocytosis. When the blood picture returned to normal following repeated transfusions and cessation of bleeding, the macrocytosis disappeared.

The most common cause of an increase in volume index with an apparent macrocytosis is pernicious anemia, in which the large cells are due to the absence of the erythrocyte-maturing factor. The bone marrow demonstrates an almost complete megaloblastic arrest, with a resultant inadequacy of proper maturation. The erythrocyte-maturing factor depends upon the interaction of the intrinsic factor of Castle, secreted by the gastric glands, and the extrinsic factor, supplied by the diet. Absence of this factor arrests maturation

of the red blood cells and causes the subsequent outpouring of relatively immature cells. As soon as the intrinsic factor is supplied by substitution of parenteral liver extract, maturation of the megaloblast proceeds normally.

One such patient, a 49-year-old housewife, sought medical advice because of "weakness and acid condition" of ten months' duration. When she was seen first her tongue was red and atrophic, but no icterus, splenomegaly, or alteration in sensation was apparent. No free hydrochloric acid was present in the stomach. Blood count was 1,350,000 red blood cells, hemoglobin 35 per cent, 3850 white blood cells, with 72 per cent neutrophils. The volume index was 1.44 and the color index 1.29. The patient responded satisfactorily to parenteral liver therapy, and in a period of several months her blood had returned entirely to normal.

If there is inadequate absorption of the erythrocyte-maturing factor, similar difficulties may be experienced. In sprue, because of the associated diarrhea, proper absorption is lacking, so that once again the erythrocyte-maturing factor is not present in adequate amounts for complete maturation of the red blood cell. An example was a 39-year-old housewife who, for two and a half years preceding admission at the Cleveland Clinic, had experienced varying degrees of diarrhea, at times reaching 15 to 20 stools daily. The stools would invariably be frothy, yellow, bulky, greasy, and foul-smelling. Complete gastrointestinal x-ray examination elsewhere failed to reveal any organic basis for the diarrhea. Severe weight loss had occurred. Atrophy of the tongue was not noted, and no splenomegaly or alteration in vibratory sense was apparent. There was no free hydrochloric acid in the stomach; total acidity was 10 units. A stool specimen revealed large amounts of neutral fatty acids and many fatty acid crystals. The glucose tolerance test was of the diabetic type. A roentgenogram of the small bowel revealed a deficiency pattern. Initial blood count revealed 3,770,000 red blood cells, 68 per cent hemoglobin, 4600 white blood cells, and 8 per cent eosinophilia. The volume index was 1.09. Under parenteral liver therapy combined with oral folic acid and vitamin and dietary management, symptoms quickly subsided, and a rapid gain in weight ensued. The blood count returned to normal.

Inadequate absorption of E.M.F. was encountered in a 50-year-old housewife with anemia and numbness of the finger tips. This patient had had a hysterectomy at the age of 31, a laparotomy for questionable intestinal obstruction at the age of 36, and another operation at the age of 46 because of "acute intestinal obstruction." Physical examination was normal except for impairment of the vibratory sense in the toes. An Ewald test upon two occasions revealed 40 units of free hydrochloric acid, with a total acidity of 60 units. Roentgenograms of the small bowel demonstrated an obstructing lesion in the proximal ileum probably secondary to previous surgery. The initial blood count revealed 2,910,000 red cells, 68 per cent hemoglobin, 5700 white cells, with a normal differential distribution. The volume index was 1.31. The patient responded slowly to the less refined parenteral crude liver extract, but she became symptom-free and her blood count returned to normal. Recently, because of fear of any future bowel obstruction, another laparotomy has been

performed, sidetracking an almost complete stenosis of the ileum associated with an ileocolic fistula which had prevented complete obstruction. She has remained entirely symptom-free, receiving liver extract every other week.

This case represents a different type of failure of absorption of the E.M.F. which may produce macrocytosis.

Still another cause of macrocytosis is that found in liver disease, in which, although an adequate amount of E.M.F. is present, improper utilization and storage takes place. In one case, a 50-year-old man with cirrhosis of the liver had experienced repeated hematemesis and tarry stools six weeks prior to admission. He had been a moderately heavy drinker of alcoholic beverages for some time, with a restricted dietary intake. His complexion was sallow, and several areas of telangiectasia were noted on the nose. The liver edge was palpable 2 fingers' breadth below the right costal margin. The bromsulfalein retention test revealed 32 per cent retention of the dye at the end of thirty minutes. The Takata-Ara test was positive. Roentgenograms of the esophagus did not demonstrate esophageal varices. Blood count revealed 2,760,000 red blood cells, 58 per cent hemoglobin, and 4500 white cells, with a normal differential distribution. The volume index was 1.29, icteric index 15. Unfortunately, this patient died following a severe episode of hematemesis before an opportunity for adequate therapy was possible.

If the liver disease is not too severe, and if excessive scar tissue is not present, a satisfactory response may usually be expected with supportive management and liver extract injections, with subsequent return of the blood picture to normal. Of course, absence of macrocytosis does not preclude the presence of liver disease.

Aplastic anemia is one of the more rare causes of macrocytosis and is believed to be secondary to failure of maturation in red cell development. The reason for such failure is not understood. The bone marrow is aplastic as in the following case: A 67-year-old man who had been engaged in the rubber industry and at times had been exposed to the fumes of benzol, had become short of breath and had developed anemia several years prior to admission. Other than considerable pallor and hepatomegaly, physical examination was negative. An Ewald test, bromsulfalein retention test, urea clearance, and roentgenograms of the chest were within normal limits. The bone marrow was completely aplastic upon two occasions and the blood count revealed 2,200,000 red blood cells, 44 per cent hemoglobin, and 1150 white blood cells with a volume index of 1.11. Therapy is of no avail in such cases.

A normal volume index can be present in pernicious anemia under certain circumstances, such as in the case of a 50-year-old colored truck driver who initially complained of epigastric pain and the passage of tarry stools intermittently for five years. Physical examination revealed a severe blood loss; the blood pressure was 84 systolic, 50 diastolic. There was diffuse tenderness throughout the abdomen. Examination of the stool was negative for occult blood three days after admission. No abnormalities were demonstrable by roentgenogram of the gastrointestinal tract. An Ewald test revealed an absence of free hydrochloric acid, with a total acidity of 12 units. The blood count

revealed 2,230,000 red blood cells, 40 per cent hemoglobin, 6450 white blood cells, and an icteric index of 15. The reticulocyte count was 1.8 per cent, with 10 nucleated red blood cells per 100 white cells. The volume index was 0.98. Study of the bone marrow revealed a megaloblastic marrow.

This patient failed to demonstrate an increase in volume index, because the microcytosis from repeated gastrointestinal hemorrhages had offset the macrocytosis of pernicious anemia. Under management by repeated transfusions and parenteral liver therapy, the patient has made an uneventful recovery.

Conclusions

Macrocytosis may be due to any one or a combination of several factors. These include lack of the E.M.F., failure of its absorption, failure of its proper utilization, or sudden release of immature cells from the bone marrow secondary to acute blood loss. The management of macrocytosis depends upon its etiology, but an effort should always be made to supply parenterally an adequate amount of E.M.F. to assure its presence in proper amounts. When macrocytosis is due to aplastic anemia, no type of therapy is of avail.

BRONCHIAL ADENOMA

DONALD B. EFFLER, M.D.
Department of Thoracic Surgery

THE earliest description of adenoma of the bronchus is attributed to Mueller,[1] who reported a case with autopsy findings in 1882. Subsequent reports have been relatively few in comparison to the number of treatises on other primary neoplasms of the bronchus. Nevertheless, with the general improvement of endoscopic and surgical technics there has been an increasing interest in the clinical and pathologic aspects of these tumors.[2] Since the possibility of cure of bronchial adenoma is so great it is important that this disorder be considered more generally in differential diagnosis and not relegated only to the thoracic surgeon and the otolaryngologist.

Clinical Picture

Adenoma of the bronchus is most commonly found in the primary divisions of the tracheobronchial tree.[3] For this reason the lesion can usually be visualized directly by the bronchoscopist. Likewise, the characteristic location of the tumor accounts for the uniformity of the symptom complex.

The majority of patients with this tumor complain of cough and hemoptysis.[4] The cough may be "dry" or productive of copious amounts of sputum, depending on the degree of parenchymal obstruction and secondary infection. There may be wheezing on the affected side due to partial bronchial occlusion.[5] Cases of so-called "unilateral asthma" should always be looked upon with suspicion and the diagnosis of intrabronchial tumor must be excluded.

Hemoptysis has been described as a cardinal sign. The bleeding may be abrupt in its onset and in its termination. It may vary in degree between blood streaking and exsanguinating hemorrhage. Usually the patients complain of intermittent hemorrhages over a period of years. They are frequently considered to have pulmonary tuberculosis and may have been treated for that disease.

The age and the sex distribution of patients with bronchial adenoma differ considerably from those with bronchogenic carcinoma. The adenoma may occur in youth; however, the majority of cases are seen between the third and the fifth decades of life. Jackson[3] reports that the patients in his series ranged between 14 and 44 years of age. Naclerio and Langer,[1] reporting Overholt's series, state that the average age of the patients was 37.4 years, whereas in bronchogenic carcinoma the average was 53.2 years. Bronchogenic carcinoma appears predominantly in men. The ratio in several large series of lung cancers ranges between 4:1 to 8:1 in favor of men, whereas in the patients with adenoma the tumor is more commonly seen in women.[1,4] Eighty per cent of Jackson's patients were women.

Occasionally the adenoma may be manifest only by symptoms of bronchial occlusion. In such patients the presenting symptoms may be dyspnea, fever, expectoration, and chest discomfort. Many patients have a history of repeated episodes of pneumonitis or atypical pneumonia. Bronchiectasis and obstructive emphysema are frequently recognized in patients who have bronchial occlusion due to adenoma.

Diagnosis

The clinical picture is usually suggestive. Roentgenograms of the thorax may outline the tumor mass. More commonly, however, there is roentgen evidence of bronchial obstruction with atelectasis or obstructive emphysema. The evidence gained from a careful history and physical examination, aided by ordinary x-ray studies, should suggest the possibility of an adenoma in the bronchus.

Bronchoscopic visualization of the tumor and tissue biopsy will afford specific diagnosis. The large majority of these tumors are located within the range of the bronchoscope. Occasionally the tumor may be peripheral and beyond the point of visualization; in such cases the presumptive diagnosis of pulmonary neoplasm is made and the suspicion of adenoma may be confirmed after pulmonary resection. The diagnostic search is not complete until bronchoscopy has been utilized.

The bronchogram may be of value in demonstrating the obstructing lesion when it cannot be visualized through the bronchoscope. In addition, iodized oil may delineate bronchiectatic segments distal to the point of obstruction. Ordinarily, however, the diagnosis of adenoma may be established without the aid of bronchography.

In the study of all suspected bronchogenic tumors, there will be times when only presumptive diagnosis can be made. Exploratory thoracotomy must then be employed. There is no place for prolonged observation in the management of these patients.

Treatment

Although there have been many approaches to the therapy of bronchial adenoma, the most widely accepted method of treatment today is surgical extirpation of the tumor and the involved pulmonary tissue. This may be accomplished by lobectomy or pneumonectomy depending on the location and the extent of the adenoma. The rate of cure is well over 90 per cent by this method and the expected mortality rate should be below 5 per cent. The majority of patients with an untreated adenoma will eventually die of the tumor regardless of whether it is benign or of the lowest grade of malignancy. The cause of death is usually attributable to suppurative disease in the obstructed parenchyma or to hemorrhage; less commonly it will be due to local invasion of the tumor and distant metastases.

Case Report

A woman, aged 49, was first seen at the Cleveland Clinic on October 15, 1948. Her chief complaints were cough and hemoptysis. History revealed that the patient had expectorated blood ever since 1928; episodes of hemoptysis had been infrequent and minor in degree, nevertheless gross evidence of bleeding had been noted on many occasions. In May 1948 the patient first noted cough and a "suffocating sensation" on bending over, with immediate relief of the latter symptom on standing or sitting erect. The cough persisted until October 1948 and was non-productive except for the intermittent bleeding.

Physical examination did not reveal objective evidence of acute or chronic disease. Examination of the chest was essentially normal; the lung fields were clear by percussion and auscultation. The fingers did not show clubbing and there was no evidence of regional lymphadenopathy. During examinations, however, the patient exhibited a persistent non-productive cough; there was no evidence of bleeding.

Roentgen studies of the chest revealed a retraction of the mediastinum to the left side. In addition there was an increased density at the left base consistent with tumor and lower lobe atelectasis. The upper half of the left lung field showed increased translucency consistent with compensatory emphysema. The initial impression was bronchial occlusion with neoplasm as the most likely cause.

On October 19, 1948 bronchoscopic examination revealed a large tumor mass in the left main bronchus that appeared to be emerging from the left lower lobe orifice (fig. 1). Tissue was obtained and the diagnosis of adenoma confirmed microscopically. On the basis of these findings exploratory thoracotomy was advised.

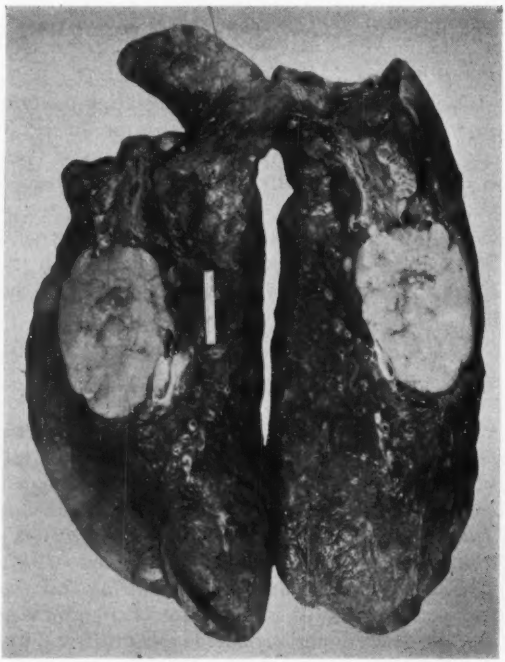


FIG. 1. Horizontal section of left lung demonstrating large encapsulated extrabronchial tumor mass. Neoplasm apparently arises in superior division of left lower lobe.

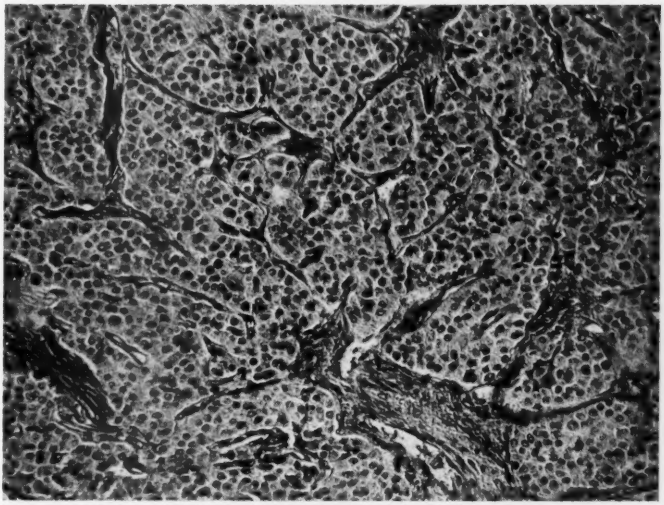


FIG. 2. Photomicrograph showing central portion of tumor (x-150).

On November 18, 1948 a left total pneumonectomy was performed. The extent of the intra and extrabronchial mass precluded a lower lobe lobectomy. The patient stood the operation well. Eight days later she was discharged from the hospital after an uneventful convalescence.

Pathologic Summary*

Pathologic examination of the left lung revealed an ovoid tumor, 6.5 cm. in greatest diameter, in the subhilar region. The main stem bronchus and the first dorsal bronchus were each obstructed by a broadbased polypoid mass in direct continuity with the main tumor in the adjoining lung tissue. The neoplasm infiltrated and replaced the dorsal bronchi, encased a large branch of the pulmonary artery, and, though demarcated from the adjoining lung parenchyma, was not encapsulated. Scattered areas of bone formation were present in the tumor. One lymph node immediately adjoining the hilar aspect of the mass was infiltrated by tumor by direct extension. Eleven other hilar nodes were not involved by neoplasm.

Histologically, the tumor was formed by small epithelial-like cells, individually and in arrangement, bearing a close resemblance to the carcinoid tumors of the intestinal tract (fig. 2). There was microscopic extension into several lymphatics and in one instance the tumor formed a cuff about a nerve. No tumor foci separate from the main mass were present in the lung.

The lower portion of the lung was collapsed and the bronchi were severely dilated and filled with thick mucus. The lung was incompletely divided by a

**Reported by Dr. J. B. Hazard, Head of the Department of Pathology.*

shallow short fissure in the lower posterior portion. One hilar node contained two yellow, partly calcified foci.

Pathologic diagnoses were: (1) So-called bronchial adenoma, carcinoid variant, of the left lung, subhilar aspect. (2) Metastasis by direct extension to one hilar lymph node; infiltration and obliteration of dorsal bronchi; intralymphatic and perineural extension. (3) Atelectasis and bronchiectasis of lower portion of the lung. (4) Old pleuritis. (5) Old tuberculosis of hilar lymph node.

Comment: Though the local infiltrative properties of this neoplasm are evident, distant foci in lungs or lymph nodes are not found. The histologic configuration is in all ways typical of the pulmonary neoplasm still best known as bronchial adenoma despite its frequently infiltrative character. Perineural extension is an unusual feature. This tumor is strikingly similar morphologically to the carcinoid tumors of the intestinal tract. Despite the fact it appears to be a malignant neoplasm because of invasiveness, so far as can be determined aggressiveness is manifest only by direct extension. Though a few of these tumors have been known to cause distant metastases, there are no present histologic criteria by which such an event may be positively predicted.

References

1. Mueller, cited by Naclerio, E. A., and Langer, L.: Adenoma of bronchus; review of 15 cases. Am. J. Surg. **75**:532-547 (April) 1948.
2. Sano, M. E., and Meade, R., Jr.: Five types of so-called bronchial adenoma; a histopathologic study. Arch. Path. **43**:235-243 (March) 1947.
3. Jackson, C. L., Konzelmann, F. W., and Norris, C. M.: Bronchial adenoma. J. Thor. Surg. **14**:98-105 (April) 1945.
4. Graham, E. A., and Womack, N. A.: Problem of so-called bronchial adenoma. J. Thor. Surg. **14**:106-119 (April) 1945.
5. Fried, B. M.: Bronchiogenic adenoma; benign tumor of bronchus. **79**:291-306 (March) 1947.

DOUBLE VENTRICULAR SHIFT IN A CASE OF CEREBRAL HEMIATROPHY

ROBERT M. GEIST, JR., M.D., and C. ROBERT HUGHES, M.D.

Department of Roentgenology

CEREBRAL hemiatrophy has always been an entity involving considerable controversy and confusion. Since its first introduction into the American literature by Dyke, Davidoff, and Masson[1] in 1933, attempts have been made to standardize the terminology. The original 9 cases presented by these authors displayed atrophy of one cerebrum and homolateral skull changes associated with varying degrees of contralateral hemiplegia, Jacksonian seizures, and mental deficiency. In all but one of the cases the onset of the illness began during the first eighteen months of life. The etiology was variable and in several cases was unknown. Roentgenography revealed a homolateral thickening of the vault with over-development of the sinuses. Air studies demonstrated hemicortical atrophy and an enlargement of the ventricular system with a shift to the atrophic side. All of the cases presented had been examined several years after the original illness.

A similar series of 9 cases was presented a few years later by Casamajor and Laidlaw.[2]

Independently at the same time Alpers and Dear,[3] in an effort to clarify the subject, suggested that the classification be broken down into primary and secondary on the basis of the age of the patient when the original illness developed. They considered it to be primary when the patient was under 3 years of age. The signs and symptoms in their 22 cases of primary hemiatrophy were essentially the same as those listed by Dyke, Davidoff, and Masson, and by Casamajor and Laidlaw.

Ross[4] presented a group of 36 patients ranging in age from 11 to 49 years. Included in his series were both primary and secondary types but he did not make any attempt at differentiation. Emphasis was placed on the varied causes which included in order of frequency: central nervous system infection, obscure, congenital, traumatic, and systemic infection.

Considerable objection has been made by Josephy[5] to this procedure of lumping together a group of varied diseases which produced atrophy. It is his contention that the term cerebral hemiatrophy should not be used as a "catch all" but should be reserved for that specific type of true atrophy described by Schob in which there is a chronic parenchymatous degeneration of the cortex. This is in contrast to the lobar sclerosis or ulegyria in which there is a destructive process with interruption of the blood supply and scar formation. Such a classification on a histopathologic basis seems much to be preferred.

Our case of hemiatrophy may be classified as a primary type which histopathologically represents an extensive hemilateral ulegyria. Many of the cases

of Dyke, Davidoff, and Masson, and others also fall in this classification. This case is believed to be unique in that the patient was examined at the time of the original causative illness and the encephalographic changes observed throughout the course of the resulting atrophy. Of particular interest is the reversal in the direction of the ventricular shift.

Case Report

A girl 15 months old had experienced episodes of high fever of short duration for two months which the parents attributed to teething. On April 11, 1947, she became acutely ill with one of these attacks of fever. She failed to respond to the usual treatment and the following day was admitted to a local hospital. At this time the child was comatose and exhibited almost continuous right-sided Jacksonian convulsive seizures lasting twenty to thirty minutes. The temperature was 106 F. There was no significant history prior to the current illness and the child had apparently been normal since birth.

Sponge baths and enemas were instituted in an effort to reduce the fever. In the course of the first day the temperature dropped to 101 F. and the convulsions ceased. Examination showed a right facial paralysis. The pupils were round and equal. The disks were not choked. A spastic right-sided paralysis was present. Spinal tap revealed normal dynamics with a normal cell count, protein and sugar. The urine was negative. The white blood cell count was 9100 with 81 per cent neutrophils. The child was placed on large doses of penicillin and sulfadiazine. Her condition remained unchanged with the temperature ranging from normal to 100 F.

On April 16, she was transferred to the Cleveland Clinic Hospital. On admission the child revealed a right hemiplegia without loss of sensation. There was no choking of the disks and reflexes were normal. Examination of the blood showed 4,120,000 red blood cells with 9.5 Gm. hemoglobin and 5275 white blood cells with a normal differential count. The Kahn test was negative. The urine and stool examinations were negative. Routine skull films were normal.

The child's condition remained unchanged and on April 18, an encephalogram was done. Forty-one cubic centimeters of clear colorless fluid were displaced with 51 cc. of air. The spinal pressure could not be measured. On analysis the spinal fluid was normal. The films showed obliteration of the cortical sulci on the left with slight displacement of the ventricular system to the right (fig. 1a). The possibility of acute cerebral edema from a cerebral infarct was considered most likely although a neoplasm could not be ruled out. The condition of the child changed little with the exception that she became more alert.

On April 30, a second encephalogram was made. Forty-eight cubic centimeters of spinal fluid were displaced with 58 cc. of air. On analysis the fluid was normal. Films showed no change from those taken on April 18. An exploratory trephine of the left parietal region was then carried out. The underlying cortex appeared normal but a cannula introduced encountered a widespread area of softening. A biopsy was made which showed severe tissue degeneration. The patient was discharged from the hospital on April 30, with the diagnosis of probable infarction.

The child was readmitted to the hospital on August 12, 1948 for follow-up study. She had shown a steady improvement throughout the year; mental development seemed normal and she was able to walk fairly well. Speech was good. However, the right arm showed only minimal recovery. On August 13 an encephalogram was again performed. Sixty cubic centimeters of fluid were displaced with 70 cc. of air. The initial pressure was 330 mm. of water. Examination of the films showed a severe left cortical atrophy with dilation of the left lateral ventricle and the third ventricle. There was a shift of the entire ventricular system to the left (fig. 1b). The diagnosis was that of cerebral hemiatrophy following infarction. The child was discharged on August 18.

a. *b.*

FIG. 1. (a) Encephalogram done April 18, 1947 showing obliteration of the cortical sulci with displacement of the ventricular system to the right. (b) A second encephalogram done August 12, 1948 showing hemiatrophy with a reversal in the direction of the ventricular shift.

Comment

We have been particularly interested in the encephalographic changes which this case of cerebral infarction demonstrates. The loss of visualization of the cortical sulci and the shift of the ventricular system to the contralateral side in the acute phase is what one would expect in view of the extensive edema and necrosis. However, the differential diagnosis between such a process and a space-filling lesion presented a problem which could not be solved definitely except by biopsy and progress encephalography. On follow-up encephalography, severe atrophy of the left cerebrum was demonstrated. The left lateral ventricle was considerably dilated and the entire ventricular system was shifted to the ipsilateral side. Even at this point when the diagnosis of cerebral infarction with atrophy was established, the actual cause of the infarction could not be determined. The possibility of an infectious etiology is plausible although purely speculative.

The degree of atrophy present at this time was measured by the method of Evans[6] in which the width of the lateral ventricles is compared to the width of the skull. We obtained a figure of .34 (normal .16 to .29). Despite the atrophy there was no associated homolateral skull thickening. Since this is believed to be a process resulting from decreased internal growth pressure, such changes would be expected to appear eventually.

The actual mechanism of ventricular shift such as was demonstrated in our case is discussed at length by Robertson and Childe,[7] and Crothers and Wyatt.[8] They are of the opinion that the shift as demonstrated in acute edema is on

the basis of expansion alone. In cerebral atrophy the shift towards the atrophic side is attributed to differential growth. They were unable to demonstrate any evidence that the shift was due to scarring or traction from adhesions.

In our opinion, this case supports the contention of Walker[9] that serial encephalograms in all types of retardation and palsies in children are of great diagnostic significance.

Summary

In a case of cerebral hemiatrophy the active and passive process is demonstrated by means of serial encephalography showing a double ventricular shift. The diagnostic significance of serial encephalography in retardations and palsies in children is illustrated.

References

1. Dyke, C. G., Davidoff, L. M., and Masson, C. B.: Cerebral hemiatrophy and homolateral hypertrophy of skull and sinuses. Surg., Gynec. and Obst. **57**:588-600 (Nov.) 1933.
2. Casamajor, L., and Laidlaw, R. W.: Convulsive states with evidence of brain hemiatrophy. Am. J. Psychiat. **96**:165-175 (July) 1939.
3. Alpers, B. J., and Dear, R. B.: Hemiatrophy of brain. J. Nerv. and Ment. Dis. **89**:653-671 (May) 1939.
4. Ross, A. T.: Cerebral hemiatrophy with compensatory homolateral hypertrophy of skull and sinuses, and diminution of cranial volume. Am. J. Roentgenol. **45**:332-341 (March) 1941.
5. Josephy, H.: Cerebral hemiatrophy (diffuse sclerotic type of Schob). J. Neuropath. and Exper. Neurol. **4**:250-261 (July) 1945.
6. Evans, W. A., Jr.: Encephalographic ratio for estimating ventricular enlargement and cerebral atrophy. Arch. Neurol. and Psychiat. **47**:931-937 (June) 1942.
7. Robertson, J. S., and Childe, A. E.: Relation of ventricular asymmetry to contracting intracranial lesions. Arch. Neurol. and Psychiat. **43**:80-89 (Jan.) 1940.
8. Crothers, B., and Wyatt, G. M.: Mechanism of displacement of ventricular system in children with atrophic lesions. Arch. Neurol. and Psychiat. **45**:246-260 (Feb.) 1941.
9. Walker, A. E.: Encephalography in children. Am. J. Roentgenol. **32**:437-456 (Oct.) 1934.

THE USE OF SEX HORMONES IN CANCER

E. PERRY McCULLAGH, M.D.
Department of Endocrinology

FOR more than a century it has been known that the only hope for cancer depends on the complete destruction or removal of the tumor cells. Consequently, when metastases have occurred cure is difficult, if not impossible, unless some method such as chemotherapy can be adapted to the task. Chemotherapy for cancer is not new; chemical treatment was employed in many forms even before the advent of modern surgery. Recently many substances have been tried experimentally for their effects upon the development of malignant tissues.[1] It seems just to say, however, that sex hormones have shown more promise than any other form of chemotherapy.

Hormonal treatment of cancer is not without grave dangers, especially if it is used in improperly selected cases. The treatment is palliative, not curative. In carefully selected cases, however, it may relieve pain, improve health, and prolong life in some patients. The mode of action of the hormones under consideration is incompletely understood, and the apparent inconsistency of results is totally unexplained. Even though cures are not produced a study of the relationship of hormones to cancer offers hope of explaining the previously mysterious natural history of the disease.

For the following statements I have drawn heavily upon the recent literature especially on the work of such investigators as Adair,[2] Farrow,[3] Nathanson,[4] Huggins,[5] and Vest[6] in this country, Haddow,[7] Fergusson,[8] and others in England.

Hormones and the Breast

The breast from birth to old age is constantly subject to endocrine factors of control. From experimental evidence we know that the duct system is developed chiefly under the action of estrogens, and progesterone acting simultaneously with estrogens is an important factor in producing lobular growth. The effect of pituitary lactogenic hormone on the production of milk has been extensively studied.

Many changes in the breast may occur under physiologic influences. These include the breast hypertrophy and production of "witch's milk" in the newborn; the frequent breast hypertrophy in puberal boys and normal breast growth in puberal girls; the cyclic changes in the female breast during the menstrual cycle; the changes in pregnancy, lactation, and of the climacteric and senescence. On the pathologic side we recognize profound changes in the breast frequently in association with certain ovarian or testicular tumors, in some tumors of the pituitary and adrenal cortex, as well as breast hypertrophy in cirrhosis of the liver, in certain instances of malnutrition, and during stilbestrol therapy for prostatic cancer. Under some circumstances mammary

enlargement occurs in association with testicular failure as well as in eunuchoid men treated with testosterone.

Although the menstrual cycle has never been shown to have any definite effect upon breast cancer, the disease frequently tends to advance with great rapidity during pregnancy and lactation. It is suspected that this is due in part, at least, to the changes in breast structure. There are a few reports of the development of human breast cancer following prolonged administration of estrogen, but as yet no proof of etiology is forthcoming. Certainly with the widespread use of estrogens one would expect more reports of breast cancer after their use if they were important as a cause.

Castration and Breast Cancer

Castration as an adjunct to the treatment of breast cancer was suggested independently by Schinzinger[9] in 1889 and by Sir George Beatson[10] in 1886. The results of such treatments have been reexamined recently. According to Adair,[11] transient beneficial response may be expected in 15 to 30 per cent of castrated patients who have advanced recurrent or metastatic disease, and little or no response is to be expected in the primary tumor or in lymph gland metastases. The patients who improve are almost entirely in the premenopausal group. X-ray castration may produce good results (fig. 1). In some in whom it fails the failure is suspected to be due to incomplete cas-

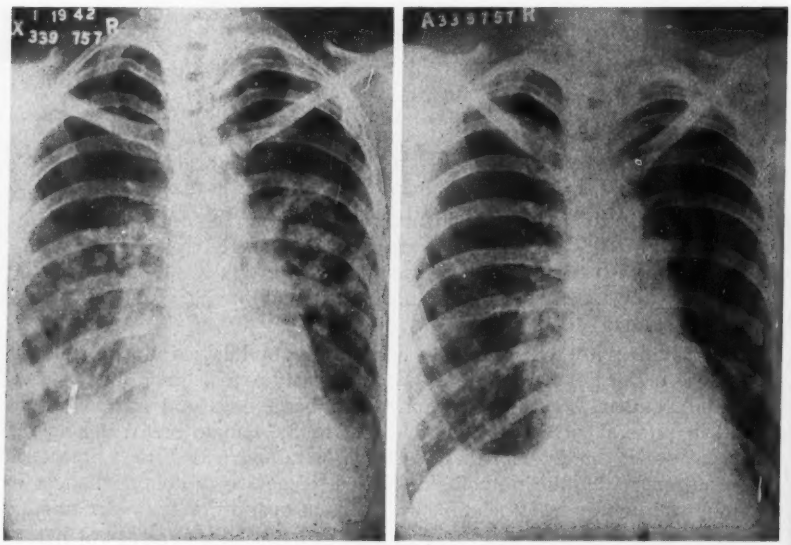


FIG. 1. Regression of metastases from breast cancer in a woman 42 years old. Six months following x-ray therapy to ovarian region. Total skin dose 1650 r.

tration effects of the x-ray. A good result is manifested by relief of pain, increase in appetite and weight, regression of bone metastases, and occasionally pulmonary metastases. Unfortunately, beneficial response is transient.

Administration of Estrogens

When it was discovered that certain carcinogenic hydrocarbons influenced the growth of experimental malignant lesions,[1] some of these substances were tried in cases of human breast cancer. It may appear absurd that the excessive rate of growth of malignant breast tissue should be decelerated by substances which at one time accelerated the development of the same tissues, but such is the case. Haddow[7] reported the results in 73 cases treated with triphenyl clorethylene, triphenylmethylethylene, and stilbestrol, all estrogens. With trichlorphenylethylene there was a favorable response in 10 of 22 patients treated, and with stilbestrol there was improvement in 5 of 14 patients treated, approximately half the patients in each group. The results were similar in both groups, namely, transient retardation or regression of the local growth with evidence of prevention of metastases.

Ten British observers have reported the value of estrogens in the therapy of breast cancer[12] on a group of 168 patients treated with stilbestrol for advanced disease. A summary of their results is presented here in tabular form.

TABLE 1
Stilbestrol in Mammary Cancer
168 Cases

Age	Under 60—100 Patients			Over 60—68 Patients		
Results of treatment in per cent of patients treated	Not improved	Improved	Spectacular improvement	Not improved	Improved	Spectacular improvement
	86	14	1	60	40	7

This table shows that striking improvement is uncommon and is limited to individuals over 60 years of age, a point of singular importance in the selection of patients.

In discussing these results, E. C. Dodds[12] made several timely suggestions: (1) that the sense of well-being be discounted and separated from actual response of the tumor; (2) that heavier doses be tried; (3) that other estrogens, such as hexestrol and dienestrol, are worth trying, and (4) that a rigid series of controls be established.

Dosage. Stilbestrol is the most widely used estrogen. The results mentioned have been obtained with oral doses of 5 to 30 mg. per day. Other synthetic estrogens, such as dienestrol and ethinyl estradiol, are being tried, but I have seen no reports of the results. To my knowledge, doisynolic acid has not been used.

Undesirable side effects of estrogen therapy may include loss of appetite, nausea, vomiting, diarrhea, and sometimes edema, which may be important when the myocardium is impaired. Menorrhagia is likely to supervene when high dosage is long continued.

Results. Good results include regression of the primary tumor, of soft tissue recurrences, and of lymph gland and pulmonary metastases. Pain from skeletal metastases may be relieved, but favorable response in them otherwise is doubtful. There is great individual variation in response, but in all instances improvement is transient.

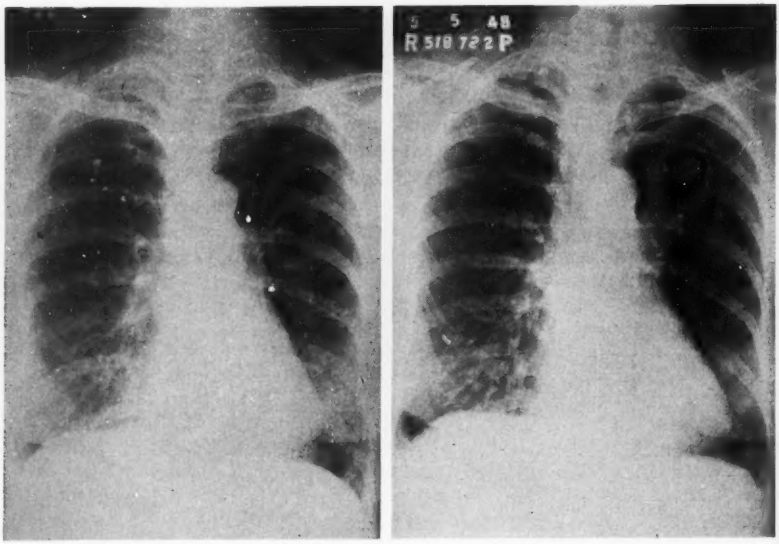


FIG. 2. Woman aged 70. Gradual but continuing decrease in pulmonary metastases from carcinoma of the breast. Eleven months after therapy with testosterone. Dose 100 mg. per day six times per week.

Dangers. The chief danger of estrogen therapy is that growth of an existing cancer may be accelerated in younger women. The Sub-committee on Therapeutic Trials of the Council on Pharmacy and Chemistry of the A.M.A.[13] warns, "Any patient who still menstruates or who has menstruated within five years should definitely not receive estrogen therapy, as it accelerates the rate of growth of the carcinoma. In no case should estrogen therapy replace radical surgery in treatment of breast cancer."

In summary, estrogens may be considered useful palliative agents for the treatment of soft tissue manifestations of advanced cancer of the breast in some older women.

The Effect of Androgens on Breast Cancer

Experimental and clinical observations regarding the effect of androgens on breast cancer have all been made within the past seven or eight years.

Results. In general, androgens have been found most useful in younger patients and in those who have skeletal metastases. As with estrogens the results are inconsistent, and there is great individual variation. Reports show that soft tissue metastases are influenced relatively little, as a rule, although again exceptions appear. One of my patients at the age of 70 had a large recurrent soft tissue mass in the subaxillary area. During testosterone therapy, 50 mg. per day over a ten-week period, this soft tissue mass disappeared till it could not be palpated, and there was a pronounced decrease in roentgenologic evidence of pulmonary metastases.

Farrow[14] mentions 2 patients, ages 37 and 60 years, respectively, who developed hypercalcemia, extension of metastases, rapid decline, and death following 400 mg. of testosterone in eight days and 250 mg. of testosterone in ten days.

Adair and Herrmann[2] reported 11 patients (women) who received doses of 50 to 200 mg. of testosterone propionate two or three times weekly. The largest total dose was 3975 mg. Four of the 11 showed improvement. In 3 recalcification of skeletal metastases was demonstrated, while in 1 hypercalcemia developed.

Symptomatic response may be dramatic. We have seen severe pain from spinal metastases disappear in two days; usually it is one to three weeks during which time a sense of strength and well-being, increased appetite, and ability to sleep without sedation appear.

Among the most impressive changes following testosterone therapy is a change in the roentgenologic appearance of skeletal metastases. In some patients areas of demineralization become denser, suggesting deposition of new bone. In some pain may disappear without any evident change in the secondary lesions. In others there may be roentgenologic evidence of remineralization, in some metastases, while other lesions in the same patient appear to increase in size and decrease in density. Unfortunately, in some patients the entire disease appears to take on increased vigor during therapy.

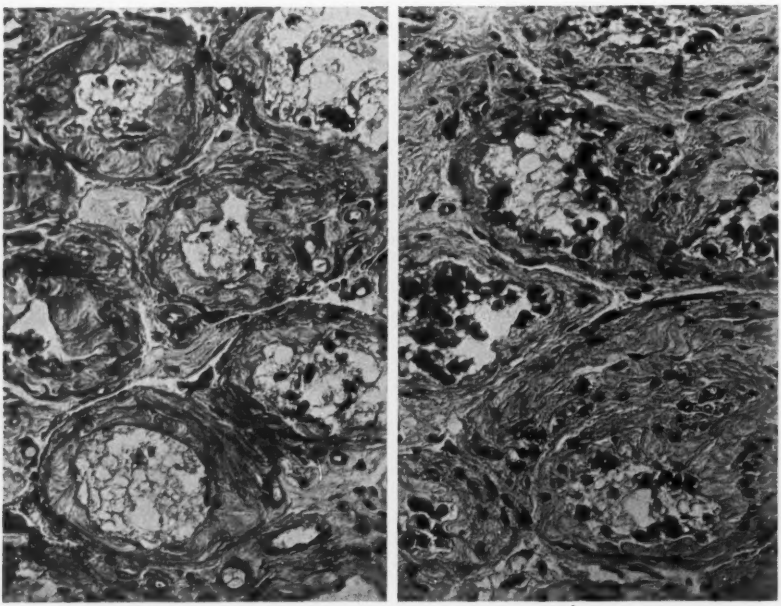
In a few patients soft tissue masses may disappear as in the patient represented in the accompanying chest x-rays (fig. 2). She received 300 mg. per week for thirteen months and is continuing to show a decrease in pulmonary metastases. During this interval a large axillary mass has completely disappeared. A small primary lesion remains palpable.

It is interesting to follow the alkaline phosphatase levels. Increases of three to five times the pretreatment range suggests healing of bony lesions. The mode of action of androgens has not been definitely ascertained but may be partially the production of other effects, such as a more direct action on cellular metabolism, in the older group.

In 20 cases we have treated, the results have been approximately as follows: In 3 symptomatic response was dramatic, and in 6 others improvement was

good, a total of 9 improved. In one of these there was definite improvement in soft tissue and pulmonary metastases. In another pain disappeared and there were striking changes in skeletal metastases, and in the third prompt to complete relief of pain from bony metastases. In the remaining 11, 3 declined rapidly and died, 1 is in extremis. In 2 the present status is unknown, and 1 was not improving and testosterone was replaced by estrogen. The remaining 4 patients have been under treatment too short a time to judge their progress.

Dosage. The dose of testosterone propionate used has varied. Earlier doses of 5 to 25 mg. were used. We have used 50 to 100 mg. six times a week in some, and in 2 patients 200 mg. daily over a period of two weeks. We have set no limit to the duration of treatment, being guided by the patient's progress only.



a. *b.*

FIG. 3. (a) Carcinoma of prostate with metastases to testes in patient aged 73. Stilbestrol therapy 2.0-4.0 mg. per day over twenty month period. (2880 mg.) (b) Patient aged 70. Twenty-five months after stilbestrol therapy 1.0-3.0 mg. per day. (1650 mg.)

Undesirable Effects. Weight gain is a common accompaniment of testosterone administration. In one of our patients, this feature caused massive painful swelling of an already swollen arm, such swelling of the neck as to make coughing and swallowing almost impossible, as well as pronounced swelling of the external genitals. Because of this, treatment was discontinued.

Nausea, headache, and malaise suggest hypercalcemia. The serum calcium should always be examined. If it is high testosterone should be given with extreme caution, if it rises to levels of 13 or above it usually should be withdrawn. Although we have seen a decline in serum calcium levels during therapy in 1 patient.

The voice usually deepens, rather extensive acne may appear, the growth of a fuzzy beard may necessitate shaving, and, even in women over 70, sexual libido may be excessively increased.

Castration for Cancer of the Male Breast

Favorable responses in carcinoma of the male breast following castration have been reported. Treves and associates[15] have reported 7 cases with a good response in 6. Strangely enough, in contrast to women, the men who showed the best results after castration were 63 years of age or older. A good response to orchiectomy has included partial regression of the primary tumor and osseous metastases. Treves believes that the effects of castration in carcinoma of the male breast may parallel the brilliant results obtained in carcinoma of the prostate following similar treatment.

Striking improvement in the local appearance in a case of cancer of the male breast twenty-two months after castration is shown by Nathanson.[16] Farrow[14] cites the case of a man in whom pronounced improvement in the primary tumor and increased density of skeletal metastases followed orchiectomy during a period of four months of postoperative observation.

Sex Hormones and Prostatic Cancer

The development and physiologic activity of the prostate gland is largely influenced by androgens. The prostate of the eunuch remains very small, its epithelium flat, and its acini almost devoid of secretion; the prostate of the adult castrate undergoes a marked reduction in size, and the acinar epithelium becomes extremely atrophic. The intimate relationship of androgens to prostatic cancer was illustrated by Moore,[17] who examined the prostates of 252 men who died between the ages of 41 and 90 and found 20 per cent malignant; yet the same author after careful search was unable to find any record of prostatic carcinoma in a patient who had eunuchoidism, eunuchism, or pituitary infantilism arising before the age of 40.

Since 1935 there has been a steadily mounting interest in the relationship between hormones and prostatic cancer. In 1935 Kutscher and Wolbergs[18] isolated prostatic phosphatase and showed that it was active in acid solution. In 1936 Gutman and Sproul[19] discovered that acid phosphatase existed in metastases from prostatic carcinoma, and it was shown that this substance did not exist in the infant prostate but was present in the adult and in the cancerous prostate.

Since that time the estimation of acid phosphatase in the blood has become a common diagnostic procedure in the estimation of the spread of carcinoma

of the prostate. Dean[20] states that there is an increase in acid phosphatase in 73 per cent of patients in whom prostatic cancer has grown through the gland capsule. Metastases may be present, however, in some cases in which the acid phosphatase level is normal. Alkaline phosphatase, on the other hand, is high in nearly all cases of metastases of prostatic cancer to the bone, indicating the activity of bone defense. It may be high also in certain liver diseases.

The experimental work of Huggins[21] also has served as a great impetus in this field. Especially impressive was his demonstration that in dogs in which the prostate was isolated from the bladder androgen treatment caused a metaplasia of the prostatic cells simulating cancer, and estrogen treatment returned the gland to normal.

Following this, orchiectomy became a popular treatment for cancer of the prostate in patients in whom complete excision of the growth did not seem feasible. Many reports are available; only 3 will be mentioned here. Dean reported the results of 31 cases treated by castration and followed for six months. The immediate results were startling. Almost without exception pain disappeared within forty-eight hours. The appetite became good, weight increased, strength returned. Soft tissue and lung metastases disappeared. The prostatic size diminished little. Some improvement in skeletal metastases was seen. The acid phosphatase levels were elevated in 19 of 26 patients in whom this estimation was made, and in 16 it fell promptly. Alkaline phosphatase tended to rise. After an average period of improvement of about eight months relapses occurred.

Huggins reported five-year results of the treatment of prostatic cancer by orchiectomy in 20 cases in which 4 had no clinical or laboratory evidence of

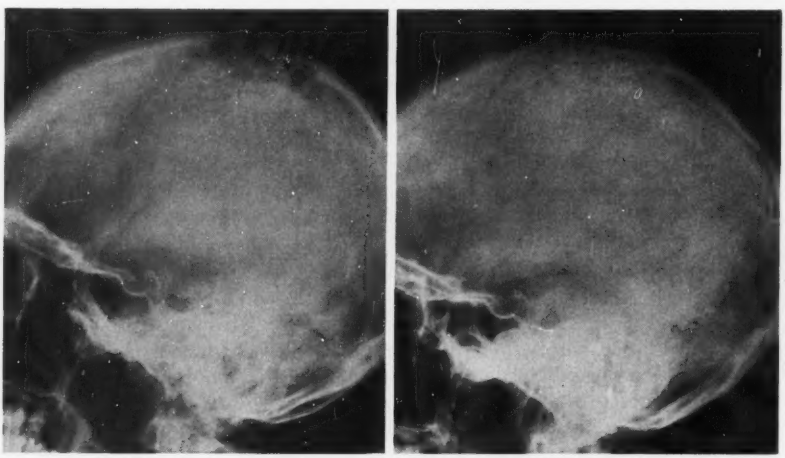


FIG. 4. Carcinoma of prostate. Age 56. After ten months' treatment with stilbestrol 2 mg. per day.

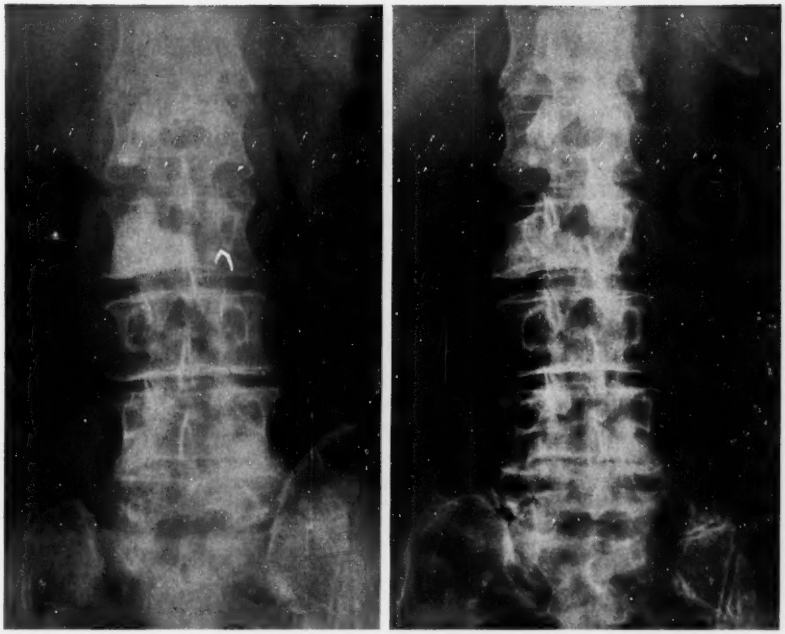


FIG. 5. Carcinoma of prostate in 78 year old patient. Changes following three years, two months stilbestrol therapy 2-3 mg. per day. Alk. phos. 2.2—acid phos. 1.4.

cancer and 1 had slowly advancing disease. All these 5 patients had had widespread metastases and elevated serum phosphatase levels at the time of orchiectomy. After five years the phosphatase levels were normal and the skeletal metastases had disappeared or were equivocal.

Vest[22] has compared the survival rate in 2 groups of 74 patients, 1 group having castration, the other not. Data from a six-year follow-up study indicates that the total dead in the noncastration group is 82 per cent, while the total dead in the castration group is 43 per cent.

Studies of hormone excretion are interesting in relation to castration. Gonadotropins rise to high levels, estrogens tend to fall, and most interesting and significant is the fact that 17-ketosteroids after an initial fall tend to rise above pretreatment levels.[23] This suggests that the adrenal androgens increase, and the suspicion arises that this may be connected with the common exacerbation which occurs. It is interesting, therefore, that no rise in 17-ketosteroids may follow the use of estrogens under similar circumstances. Also it is to be anticipated that stilbestrol therapy once started and causing severe testicular damage will in turn cause a pituitary hyperactivity greater than that before treatment if stilbestrol is subsequently discontinued.

Estrogens in Prostatic Cancer

More recently the trend has been away from castration and toward estrogen therapy for inoperable prostatic cancer. The mechanism of its action, as shown by hormone excretion studies, is quite different from that of castration. When stilbestrol is given the urinary estrogens rise by virtue of the excretion of the administered drug, urinary gonadotropin levels fall, and androgen levels, as judged by urinary 17-ketosteroids, fall. In 9 patients studied by Dean the pretreatment level of 17-ketosteroids averaged 8.9 mg. of androsterone equivalent, and the post-treatment level after doses of 2 to 5 mg. per day of stilbestrol averaged 5.4 mg.

Profound degenerative changes occur in the testis. The gametogenic elements atrophy, the basement membrane becomes thickened, and repeated biopsies have shown a decline in the apparent activity of the Leydig cells (fig. 3, a and b).

Dosage. Stilbestrol is commonly used in this country in doses of 1 to 5 mg. per day, while in England some workers[24] have given as much as 30 mg. per day. I am inclined to believe that 3 mg. per day or less is likely not to be fully effective, since we have found 3 patients taking 2.0 mg. daily in whom the gonadotrophins were not depressed below normal range. Increase of stilbestrol dosage to 5.0 and 6.0 mg. per day, respectively, depressed urinary gonadotropins to subnormal levels of less than 6 mouse units per day (table 2).

TABLE 2

Hormone Assays in Relation to Stilbestrol Therapy in Prostatic Cancer

Age	Stilbestrol Daily Dose mg.	Duration of Therapy	Other Treatment	Urinary gonadotropins m.u. per day	Urinary 17-K.S. mg. ketonic
73	1.0	4 mos.	Resection	6	
67	2.0	6 mos.	Castration	26-52	
71	2.0	6 mos.		26-52	4.8
	6.0	3 wks.		6	5.8
63	2.0	3 mos.		13-26	
	5.0	2 mos.		6	

(Normal urinary gonadotropins 13-105 mouse units daily)

Results. In general the results of treatment with stilbestrol, though slower, are otherwise equal or superior to those following castration. Symptoms are as well controlled, and in many instances large osteolytic lesions become densely remineralized (fig. 4). Osteoblastic lesions may become more dense, but whether or not this means healing in terms of cancer growth is not easy to determine by roentgenologic appearance. After a period of seven or eight months' improvement most patients have had relapses. In one case of osteoblastic

metastases of the spine, the patient outlived his prostatic carcinoma to die a cardiac death at the age of 78 years (fig. 5).

The untoward effects of stilbestrol therapy in men may include nausea, vomiting, and in some muscle pains and edema. Complete impotence is the rule, the nipples and areolae become dark, and a rather striking degree of gynecomastia appears. Malignant tumors of the interstitial cells of the testis have been reported in the estrogen-treated mouse,[25] but nothing comparable to this has been suggested in man.

Castration and estrogen treatment for prostatic cancer is palliative, not curative. It is a useful adjunct to treatment in properly selected cases but should never replace surgery where surgery holds any promise of a cure. At the present time it must be considered experimental and a hopeful approach to new avenues of study.

To quote Alexander Haddow[26], "It is indeed true that those who have considered the matter most thoroughly are under the least illusion as to its practicability. That the subject will continue to be investigated, quite regardless of success, is, however, equally true and it must therefore be our duty to stimulate the process as far as possible, while at the same time never failing to underline its inherent and therefore inescapable difficulties. The slight advances of the past few years are, however, more than were accomplished in any previous period, and it is surprisingly likely—and very much to be hoped for—that a review such as the present will comparatively soon be out of date."

References

1. Haddow, A.: Influence of certain polycyclic hydrocarbons on growth of Jensen rat sarcoma. Nature **136**:868-869 (Nov. 30) 1935.
2. Adair, F. E., and Herrmann, J. B.: Use of testosterone propionate in treatment of advanced carcinoma of breast. Ann. Surg. **123**:1023-1035 (June) 1946.
3. Farrow, J. H.: Effect of sex hormones on skeletal metastases from breast cancer. Endocrinology of Neoplastic Disease. A Symposium, edited by Twombly, G. H., and Pack, G. T. (New York: Oxford University Press, 1947) p. 179-193.
4. Nathanson, I. T.: Endocrine aspects of human cancer. Recent Progress in Hormone Research. Vol 1. edited by Pincus, G. (New York: Academic Press, 1946) p. 261-291.
5. Huggins, C., and Hodges, C. V.: Studies on prostatic cancer; effect of castration, of estrogen and of androgen injection on serum phosphatase in metastatic carcinoma of prostate. Cancer Research **1**:293-297 (April) 1941.
6. Vest, S. A., and Frazier, T. H.: Survival following castration for prostatic cancer. J. Urol. **56**:97-111 (July) 1946.
7. Haddow, A., Watkinson, J. M., and Paterson, E.: Influence of synthetic oestrogens upon advanced malignant disease. Brit. M. J. **2**:551-556 (Oct. 19) 1946.
8. Fergusson, J. D.: Carcinoma of prostate treated with oestrogens. (Hunterian lecture, abridged) Lancet **2**:551-556 (Oct. 19) 1946.
9. Schinzinger, A.: Über Carcinoma Mammae. Bericht über die Verhandlungen der deutschen Gesellschaft für Chirurgie, XVIII, Kongress. Centralbl. f. Chir. **16**:55, 1889.
10. Beatson, G. T.: On treatment of inoperable cases of carcinoma of mamma; suggestions for new method of treatment with illustrative cases. Lancet **2**:104, and 162, 1896.
11. Adair, F. E., Treves, N., Farrow, J. H., and Scharnagel, I. M.: Clinical effects of surgical and x-ray castration in mammary cancer.

12. Discussion on advanced cases of carcinoma of breast treated by stilbestrol. Proc. Roy. Soc. Med. **37**:731-736, 1944.
13. Estrogens and androgens in mammary cancer. Council on Pharmacy and Chemistry; Subcommittee on Steroids and Cancer. J.A.M.A. **135**:987-989 (Nov. 15) 1947.
14. Farrow, J. H.: Effect of sex hormones on skeletal metastases from breast cancer. Endocrinology of Neoplastic Diseases. A Symposium, edited by Twombly, G. H., and Pack, G. T. (New York: Oxford University Press, 1947) p. 187-188.
15. Treves, N., Abels, J. C., Woodard, H. Q., and Farrow, J. H.: Effects of orchiectomy on primary and metastatic carcinoma of breast. Surg. Gynec. and Obst. **79**:589-605 (Dec.) 1944.
16. Nathanson, I. T.: Hormonal alteration of advanced cancer of breast. S. Clin. North America **27**:1144-1150 (Oct.) 1947.
17. Moore, R.: Symposium on Endocrinology of Neoplastic Diseases; Benign hypertrophy and carcinoma of prostate; occurrence and experimental production in animals. Surgery **16**:152-167 (July) 1944.
18. Kutscher, W., and Wolbergs, H.: Prostataphosphatase. Ztschr. f. physiol. Chem. **236**: 237-240, 1935.
19. Gutman, E. B., Sproul, E. E., and Gutman, A. B.: Significance of increased phosphatase activity of bone at site of osteoplastic metastases secondary to carcinoma of prostate gland. Am. J. Cancer **28**:485-495 (Nov.) 1936.
20. Dean, A. L., Woodard, H. Q., and Twombly, G. H.: Endocrine treatment of cancers of prostate gland. Surgery **16**:169-180 (Aug.) 1944.
21. Huggins, C.: Prostatic cancer treated by orchiectomy; 5-year results. J.A.M.A. **131**:576-581 (June 15) 1946.
22. Vest, S. A., and Frazier, T. H.: Survival following castration for prostatic cancer. J. Urol. **56**:97, 1946.
23. Scott, W. W., Vermeulen, C.: Studies on prostatic cancer; excretion of 17-ketosteroids, estrogens, and gonadotrophins before and after castration. J. Clin. Endocrinol. **2**:450-456 (July) 1942.
24. Cox, H. T.: Treatment of carcinoma of prostate by periurethral resection and stilboestrol. Brit. M. J. **2**:191-194 (Aug. 10) 1946.
25. Hooker, C. W., Gardner, W. U., and Pfeiffer, C. A.: Testicular tumors in mice receiving estrogens. J.A.M.A. **115**:443-445 (Aug. 10) 1946.
26. Haddow, A.: Note on chemotherapy of cancer. Brit. M. Bull. **4**:417-426, 1947.

THROMBOPHLEBITIS

FAY LE FEVRE, M.D.
Department of Cardiorespiratory Disease

THE prevention, recognition, and early treatment of thrombophlebitis is important because of its relation to two significant medical conditions: (1) pulmonary embolism; and (2) chronic venous insufficiency. Thrombophlebitis may complicate medical, surgical and obstetrical cases. The incidence of thrombophlebitis during recent years appears to be on the increase which probably is due to the greater number of patients undergoing surgery and also to the extent of surgical procedures.

Certain types of thrombophlebitis do not cause the serious complications mentioned; therefore it is desirable to outline a simple classification so that the more serious types can be readily differentiated.

Classification

(1) **Local Thrombophlebitis.** In this classification we include thrombophlebitis involving the superficial veins, resulting from the injection of intravenous materials which have acted as an irritant. The mercurial diuretics, arsenicals, and materials used in x-ray diagnosis may result in a local chemical thrombophlebitis when injected. Superficial thrombophlebitis may follow trauma to an extremity. Large varicose veins may become thrombosed and areas of phlebitis ensue.

In the presence of inflammatory and suppurative lesions, local areas of thrombophlebitis secondary to these conditions may occur. Where severe arterial occlusion exists, local areas of thrombophlebitis may develop, particularly if there is a gangrenous condition and an area of demarcation. These forms of thrombophlebitis are usually local in nature and secondary to some specific condition. They do not usually result in complications other than local distress.

(2) **Primary Thrombophlebitis.** In this group we classify recurrent idiopathic thrombophlebitis or thrombophlebitis migrans, the etiology of which has not been determined. We also include a thrombophlebitis frequently associated with thromboangiitis obliterans. Thirty to 40 per cent of cases of thromboangiitis obliterans have, at some time during the course of the disease, superficial migrating thrombophlebitis. This may be one of the earliest clues to the diagnosis.

(3) **Secondary or Complicating Thrombophlebitis.** This group is the most important, inasmuch as it includes complications of pulmonary embolism and chronic venous insufficiency. Secondary thrombophlebitis may occur postpartum, postoperatively, and following medical illnesses of infectious or

non-infectious nature. This type of thrombophlebitis may be associated with blood dyscrasias, particularly polycythemia and leukemia, and in addition, with neoplastic disease.

Etiology of Thrombophlebitis

The specific cause or causes of thrombophlebitis of the secondary or complicating type have not been determined. There seems to be a greater incidence of this condition during winter months and in the Northern states. A familial or constitutional tendency and obesity frequently appear to be influencing factors. Thrombophlebitis of this type is more prevalent in patients over 40 years of age.

Three main theories exist concerning the development of thrombophlebitis:

(1) Patients confined to bed for any length of time experience increased pressure on the veins of the calf and the endothelial cells of the vein wall may adhere. These injured cells become roughened and act as a nidus for a thrombus.

(2) Patients recumbent during the course of an illness or postoperatively, undergo retardation of the blood flow. This may be increased by the patient assuming certain positions in bed, such as Fowler's position, whereby the pressure in the groin is increased and the retrograde flow of blood decreased. It is assumed that certain degrees of vasospasm induced by the use of tobacco may further retard the blood flow.

(3) Certain changes in the chemical nature of the blood occur particularly postoperatively. There is an increase in viscosity, fibrinogen and calcium content, as well as an increase in members of white cells and thrombocytes. There is a tendency to agglutination and changes in the protein chemistry, all of which may be important in the cause of thrombophlebitis.

Diagnosis of Secondary Thrombophlebitis

The diagnosis of secondary thrombophlebitis is often difficult, but if certain features are observed early precautionary measures may be taken. Mild general constitutional reactions may occur from six to fourteen days postoperatively and include an unexplained rise in temperature, pulse, and respiration. Following the onset of these reactions the patient may complain of some localized pain in the calf area and tenderness to palpation. A positive Homan's sign may be present although this is not always the case. Slight edema may exist and there may be minimal dilitation of the superficial veins.

Laboratory aids are of little assistance. A slight elevation in the sedimentation rate and leukocyte count may be present and there may be changes in the clot retraction time. These indications are not diagnostic but are helpful adjuncts in questionable cases. Venography may be used in cases of doubt.

The differential diagnosis of acute iliofemoral thrombophlebitis, acute arterial occlusion, and acute lymphangitis must be considered. These points are summarized in the table.[1]

Differential Diagnosis

	Acute Ilio-Fem. Throm. Phlebitis	Acute Arterial Occlusion	Acute Lymphangitis
Size of Limb	Enlarged	Shrunken	Enlarged
Color	Normal Slightly Cyanosed	Pale-Mottled	Red
Temperature	Normal	Low	High
Sup. Veins	Prominent	Collapsed	Normal
Arterial Pulses	Normal	Absent	Normal
Chills	Rare	Absent	Usual
Fever	Moderate	Absent	High

Treatment of Secondary Thrombophlebitis

In summarizing the treatment of secondary thrombophlebitis we must consider measures for the prevention of this condition. Careful surgical technique is, of course, one of the most effective. The incidence of phlebitis is much higher following extensive surgical procedures where there has been, either by necessity or carelessness, considerable trauma to the tissue. Pressure on the legs, particularly, should be avoided postoperatively, and the patient urged to move his limbs frequently during the day and take breathing and leg exercises. The extremities should be lightly massaged unless contraindicated by some other condition. Abdominal compression and abdominal binders are better avoided, and the patient should not be kept in Fowler's position for any length of time unless necessitated by other complications. The fluid intake should be adequate and any complicating infection treated promptly.

Early postoperative ambulation is advised and generally advocated. This should be construed as standing and taking a few steps as early as possible.

Immediate Local Care of the Extremities

When secondary thrombophlebitis occurs the extremity involved should be elevated. Care should be exercised in the use of pillows as they frequently slide underneath the knee and create an additional obstruction.

We recommend the continuous use of moist heat as the most effective application. Before applying heat the arterial circulation should be evaluated as heat may be harmful in the presence of arterial insufficiency. Heat should be applied and the extremity elevated for a period of forty-eight hours after which motion may be initiated. A supporting gum rubber bandage is the most practical type of support and should be worn for a minimum period of three months, regardless of whether or not residual edema is occurring.

Proper follow-up care should include adequate rest, support, the correction of obesity, if present, and the exclusion of tobacco.

Anticoagulant Therapy

This type of treatment should be incorporated immediately upon making the diagnosis of secondary thrombophlebitis. The intermittent method of heparin administration can be used, prescribing 50 mg. of heparin intravenously every three to four hours for a period of forty-eight hours. Immediately upon starting treatment, 300 mg. of dicumarol may be given orally the first day and 200 mg. the second day.

Daily prothrombin studies must be made at least three hours after an administration of heparin in order that a true prothrombin concentration time be determined. If the prothrombin concentration is above 30 per cent, an additional 100 mg. is given daily. The daily dose if required may vary from 50 mg. to 300 mg. Body weight is not related to dosage in the adult. About 5 per cent of patients are resistent to dicumarol. If prothrombin concentration is between 20 and 30 per cent, dicumarol is withheld. Anticoagulant therapy should be given for a period of three weeks and then discontinued if there are no complications.

Contraindications

The contraindications for using dicumarol must always be clearly recognized. They may be summarized:

1. In renal disease the effect of dicumarol may be abnormally prolonged and difficult to control and therefore should not be used.

2. In ulcerative lesions and open wounds including ulcerative colitis, and also in patients undergoing tube drainage of viscera.

3. In patients with recent operations on the brain or spinal cord hemorrhage might be disastrous.

4. In deficiency of vitamins C or K; in liver disease with prothrombin deficiency; and in blood dyscrasias or purpura.

5. In subacute bacterial endocarditis because the hemorrhagic tendency is increased.

6. In patients with hypertension having retinopathy.

Treatment for Hemorrhage

If the prothrombin concentration falls below 10 per cent, 20 to 40 mg. of vitamin K should be given intravenously at once and dicumarol withheld until the prothrombin concentration rises to 30 per cent; then it should be used in smaller doses.

If bleeding occurs 60 mg. of vitamin K and 500 cc. of fresh citrated blood should be given intravenously.

Vein Ligation and Thrombectomy

Surgical procedures have been widely used in the prevention of pulmonary embolism. If an exact differential diagnosis between phlebothrombosis and thrombophlebitis could be made, it would seem logical to employ vein ligation and thrombectomy in phlebothrombosis. In our experience, this differentiation has not been possible and excellent results have been obtained using the anticoagulant method. Therefore, we have preferred this to vein ligation. However, final conclusions on the relative merits of these procedures are not yet possible.

Perivertebral Nerve Block

Lumbar sympathetic nerve block with procaine hydrochloride has been used in the treatment of thrombophlebitis. It has been thought to be helpful in relieving vasospasm and pain. It is difficult to evaluate the merit of this procedure. It should not be used when anticoagulant therapy is being employed, as serious complications may ensue.

Summary

A simple classification of thrombophlebitis stresses secondary thrombophlebitis as the essential cause of two serious medical complications, namely pulmonary embolism and chronic venous insufficiency. If secondary or complicating thrombophlebitis can be diagnosed early and precautionary measures taken, a large majority of the complications can be prevented.

Reference

1. Allen, E. V., et al.: Peripheral Vascular Disease (Philadelphia: W. B. Saunders Company 1946).

REIMPLANTATION OF THE URETER INTO THE BLADDER

J. G. WARDEN, M.D., and C. C. HIGGINS, M.D.
Department of Urology

THE operation of reimplantation of the ureter into the bladder has undergone a stormy course of criticism before being accepted as a sound surgical procedure. It may not have been frequently advocated, primarily because there was no satisfactory method of evaluating the status of the upper urinary tract and the end results without subjecting the patient to retrograde pyelography which might be unsatisfactory. However, with the advent of intravenous urography, a simple yet relatively innocuous procedure may be used to evaluate with accuracy those cases that can be submitted to this type of operation. Because of the increased number of cases amen-

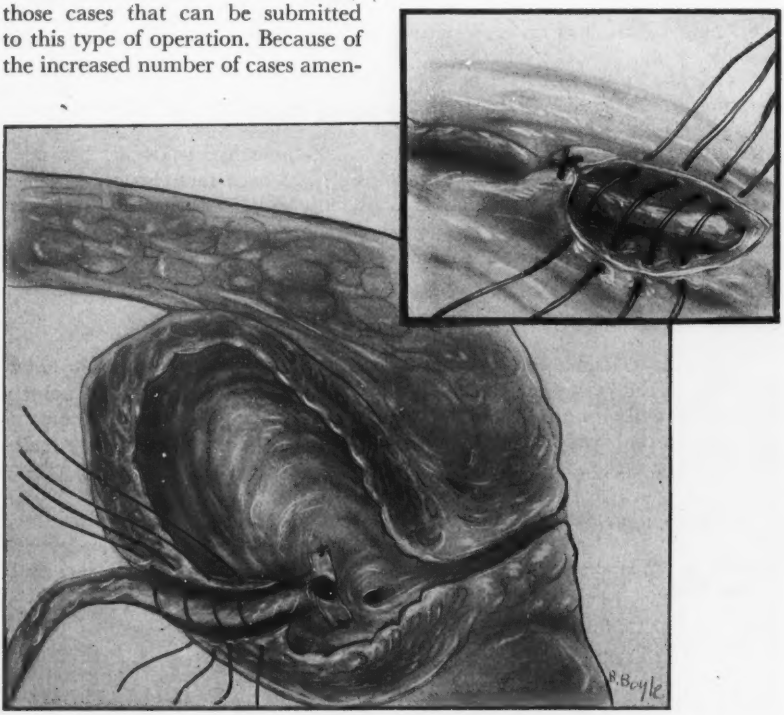


FIG. 1. Parasaggital section showing ureter in trough with sutures in place. Catheter not shown. Inset shows ureter from lateral view with sutures in place.

able for this type of surgical procedure observed recently by one of us (C. C. H.) at the Cleveland Clinic, a review of the results seems indicated.

Indications

Gynecological surgery has frequently been followed by complications necessitating reimplantation of the ureter. In recent years the increased use of combined abdominoperineal resection of the colon has also brought numerous cases to the urologist for which this surgical procedure was indicated.

A summary of indications for implantation is as follows:

1. Traumatic injuries to the lower ureter, e.g.
    a. Complicating hysterectomy.
    b. Complicating abdominoperineal resections.
    c. Complicating manipulation of ureteral stones.
    d. Complicating ureterolithotomy.
    e. Complicating ruptured bladder.
    f. Gunshot wounds.

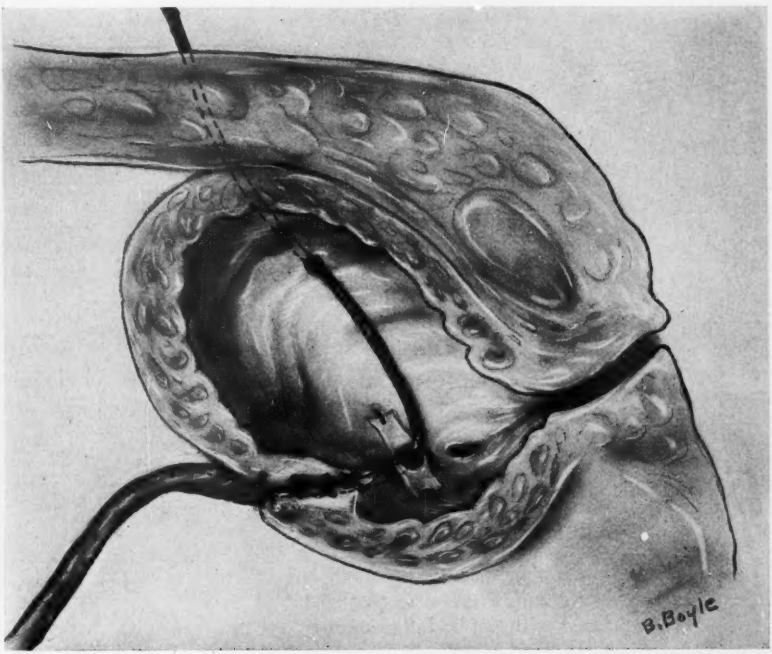


FIG. 2. Parasaggital section showing suture line closed. Ureteral catheter in place.

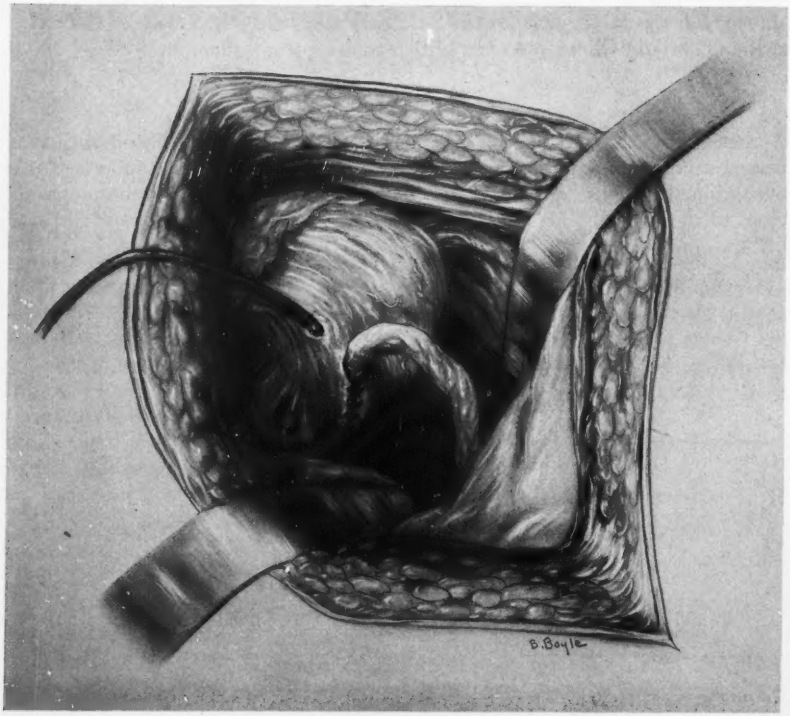
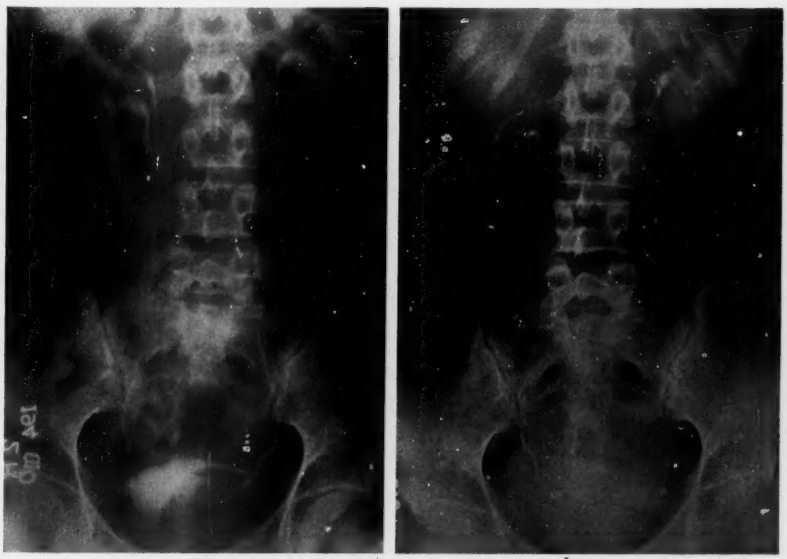


FIG. 3. Diagram demonstrating left reimplanted ureter with indwelling ureteral catheter through bladder wall.

2. Embryologic malformation of the lower ureter
   a. Ectopic ureter.
   b. Congenital ureteral valves.
   c. Stricture of the ureter.
   d. Certain ureteroceles.
   e. Ureteral diverticula.
3. Neoplastic involvement of the lower ureter
   a. Bladder neoplasms in close proximity to the ureteral orifice.
   b. Benign ureteral tumors.
4. Inflammatory involvement of the lower ureter
   a. Coexisting with ureteral stones.
   b. Associated with pelvic inflammatory disease.
5. Miscellaneous factors involving the lower ureter
   a. Bladder diverticulum involving a ureteral orifice.

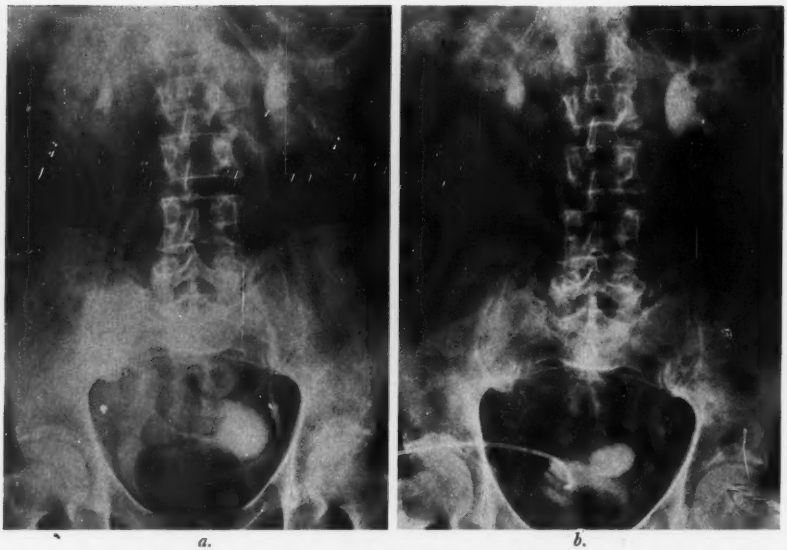
Before deciding to employ ureteral implantation, a urologic investigation is of paramount importance. A complete history and physical examination may reveal associated pathologic entities such as disseminated carcinomatosis, low cardiac reserve, or advanced arteriosclerosis thereby making such a procedure hazardous. Cystoscopic examination is important in detecting a suitable site for implantation in the bladder. An attempted retrograde pyelography should be performed because of the valuable information to be gained by this study. At the time this is done specimens of urine may be collected for culture so that preoperative and postoperative chemotherapy will be specific in case of bacterial invasion. But by far the most important procedure for evaluation of the urinary status is the intravenous urogram. By this method it can be ascertained whether the renal and ureteral damage is serious enough to contraindicate reimplantation. The location of the ureteral stricture, the presence of ureteral anomalies, and the distance of the normal ureter from the bladder wall can all be determined by urographic study.

Further aids in evaluation of the urinary status consist of the injection of methylene blue into the bladder and intravenous injection of indigo carmine. By these two methods it can be determined whether a constant urinary fistula originates from the ureter or from the bladder.



a. *b.*

FIG. 4. (a) Preoperative film. Intravenous urogram showing severe bladder defect produced by bladder neoplasm. (b) Postoperative urogram showing normal urinary tract after left ureteral reimplantation.



a. *b.*

FIG. 5. (a) Preoperative urogram showing dilation of lower left ureter by obstructing bladder neoplasm. Coexisting diverticulum. (b) Postoperative urogram showing normal urinary tract after reimplantation of left ureter and excision bladder tumor. Note cystostomy tube and bladder diverticulum.

Procedure

Although no single operative procedure is applicable to all cases, a method not unlike the Coffey I method of ureterointestinal transplantation has been used in this group.

The abdominal wall is entered through a muscle splitting pararectus incision. The peritoneum is dissected medially from the lateral abdominal wall and the ureter is isolated. The latter is freed from surrounding tissues, great care being utilized to preserve its blood supply. The ureter is freed distally as far as is practicable and is then clamped and the distal end ligated. The proximal end of the ureter is then cut on the oblique and a No. 6 ureteral catheter inserted into the renal pelvis and anchored to the ureter (figs. 1, 2, 3).

The bladder is dissected free from the surrounding tissue. On the lateral side of the bladder, as near the previous ureteral orifice as possible, Allis clamps are applied and a trough incision is made down to the mucosa. The trough is further prepared by peeling the muscle layer from the mucosa for a distance of 1 cm. At the inferior end of the trough a stab incision is made through the mucosa and the ureteral catheter and ureter are pulled through for a distance of 1 inch into the lumen of the bladder. At this point the ureteral stump end is anchored by the use of 000 chromic catgut sutures through the mucosa, submucosal and muscular layers of the bladder. Several 00 chromic sutures are

placed through the ureteral adventitia and bladder mucosa for further support of the anastomosis.

Extreme care is exercised so to avoid placing undue tension on the suture line by a taut ureter.

The ureteral catheter is brought through a minute stab wound through the lateral bladder wall and out through the incision. A Penrose drain is placed down to the ureterovesical junction, and the abdominal wall closed with stainless steel sutures. A No. 22 balloon indwelling catheter is placed through the urethra into the bladder.

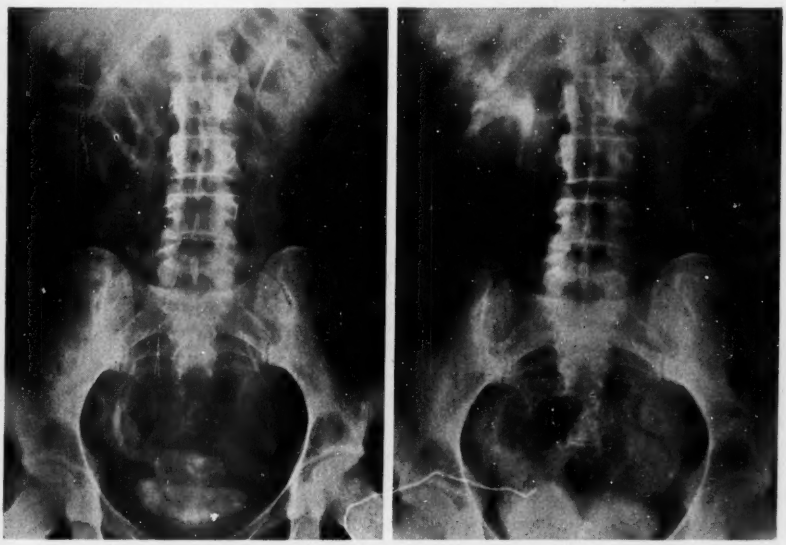
The following brief resume of case histories demonstrates the results obtained by using the above technic.

Case Reports

Case 1. A 20 year old white woman entered Cleveland Clinic on February 2, 1937 complaining of pain in the lower abdomen. The pain was dull in character, and aggravated by walking. For the past six months she had had nocturia two to three times but no hematuria or other urinary symptoms.

Physical examination did not disclose any serious abnormalities. There was some suprapubic tenderness to palpation over the abdomen.

Intravenous urogram was reported as normal, with the exception of a filling defect involving the left lateral wall of the bladder.



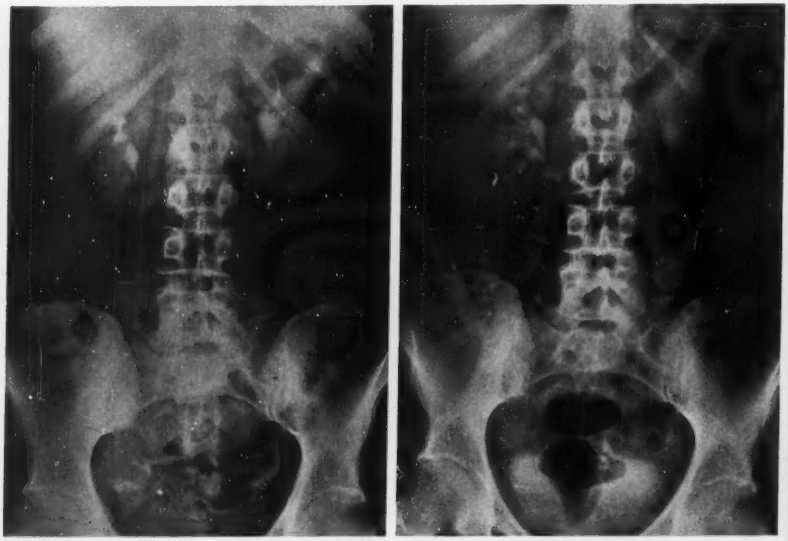
a. *b.*

FIG. 6. (a) Preoperative urogram showing right ureter draining into vagina. (b) Postoperative film after right ureteral reimplantation. Normal upper urinary tract.

Cystoscopy revealed what was thought to be a large extravesical tumor, filling two-thirds of the bladder, and involving the left ureteral orifice. Because of the massive intravesical intrusion, suprapubic exploration was performed. After exposing the bladder wall a solid tumor was found involving the muscle walls, extending from the left ureteral orifice to nearly the vesical orifice. By means of sharp dissection a partial cystectomy was performed and the ureter then implanted into the bladder wall. The postoperative course was without complications and the indwelling ureteral catheter was removed on the seventeenth day. The pathologic diagnosis was lymphosarcoma of the bladder.

A recent urogram, eleven years after operation, shows an essentially normal urinary tract (fig. 4). Repeated cystoscopic examinations have revealed no recurrence of neoplasm.

Case 2. A 65 year old white man entered the Cleveland Clinic on April 14, 1947 with a history of hematuria of two weeks' duration, accompanied by obstructive vesical neck symptoms.



a. *b.*

FIG. 7. (a) Preoperative urogram showing no dye in bladder. (b) Postoperative urogram after bilateral ureteral implantation showing normal upper urinary tract.

Physical examination revealed a well developed patient with no gross abnormalities. Cystoscopy disclosed a papillary, egg sized neoplasm immediately adjacent to the left ureteral orifice.

The intravenous urogram revealed normal kidney function, and the lower left ureter was dilated. The cystogram showed coarse trabeculation with several large diverticula. There was 450 cc. of residual urine.

Diagnosis was carcinoma of the bladder and hypertrophy of the prostate.

On April 24, 1947 a suprapubic excision of the bladder tumor and adjacent muscular wall was performed. The ureter was reimplanted into the bladder using the previously described procedure. A cystostomy tube was left in place, the ureteral catheter removed on the seventeenth postoperative day, and the patient was discharged from the hospital. The pathologic diagnosis was papillary transitional cell carcinoma of the bladder grade II.

The patient was readmitted to the hospital two months later and a transurethral resection of the prostate was performed.

Since operation the bladder has been examined every three months for neoplasm recurrences and at the same time ureteral dilations have been performed. There has been no recurrence and the upper urinary roentgenograms are normal (fig. 5).

Case 3. A 37 year old white woman was admitted to the Cleveland Clinic in 1947 with a history of continuous urinary drainage through the vagina following a complete abdominal hysterectomy performed six months previously. A repair operation had been instituted elsewhere two months prior to her admittance but this had been unsuccessful. General physical examination revealed no gross abnormalities.

Intravenous urogram showed enlargement of the right renal pelvis with tortuosity of the right ureter. The remainder of the urinary tract was normal.

Cystoscopic examination revealed a normal bladder with no evidence of fistula. A right ureteral catheterization disclosed an impassable obstruction approximately 3 cm. up the ureter. Methylene blue injected into the bladder did not appear on a vaginal pack but indigo carmine administered intravenously appeared on a vaginal pack in four minutes in excellent concentration. The left ureter was catheterized without difficulty.

Diagnosis was ureterovaginal fistula.

On February 4, 1948 through a suprapubic approach the right ureter was excised and reimplanted into the bladder by the method described.

Postoperative course was without complications and the indwelling ureteral catheter was removed on the fourteenth postoperative day, the urethral catheter was removed on the sixteenth day and the patient discharged on the seventh postoperative day.

At monthly intervals ureteral dilations have been performed until a normal urogram was obtained on the fifth postoperative month (fig. 6).

Case 4. A 51 year old white woman was admitted to the Cleveland Clinic on June 4, 1948 with a history of having had a hysterectomy performed elsewhere ten days previously for fibroids of the uterus. Immediately after operation total urinary incontinence was observed, and the patient had no desire to void.

Physical examination revealed a moderately obese white woman, with no gross abnormalities.

Cystoscopy did not show bladder fistula, but an attempt to catheterize the ureters met bilateral obstructions at approximately 2 cm. up the ureters. Methylene blue injected into the bladder did not appear in the vagina. However, intravenous injection of indigo carmine appeared in three minutes in the vagina in good concentration.

Intravenous urogram showed a normal upper urinary tract but both ureters revealed dilation in the lower thirds.

Vaginal examination disclosed excoriation of the mucosa and urinary seepage into the dome of the vagina.

Diagnosis was bilateral ureterovaginal fistula.

On June 12, 1948 the right ureter was implanted into the bladder and the indwelling ureteral catheter was removed on the thirteenth postoperative day. One month later a left ureteral implantation was performed and the indwelling ureteral catheter was removed on the sixteenth postoperative day. The patient was discharged from the hospital with excellent urinary control.

An intravenous urogram taken three and one-half months later shows essentially a normal urinary tract (fig. 7).

Summary

Reimplantation of the ureter into the bladder is a sound surgical procedure with which excellent results can be obtained. However, certain fundamental principles must be followed if failures are to be avoided.

A preliminary physical examination and thorough urologic investigation, including intravenous urogram, cystoscopy, and retrograde study is essential.

The particular operative method is probably immaterial provided adequate blood supply to the ureter is retained; the trough principle utilized, and a cuff of ureter is allowed to project into the bladder, without tension, for approximately 1 inch. The site of implantation is preferably near the original ureteral orifice and the importance of adequate splinting of the new ureterovesical junction with an indwelling ureteral catheter for a period of two weeks cannot be overemphasized. Complete relaxation of the bladder by use of a urethral catheter favors healing of the ureterovesical junction by further immobilization. Finally, drainage of the perivesical space with a Penrose drain to prevent collections of blood and tissue fluid at the anastomosis site is desirable.

MESENTERIC CYST WITH INTESTINAL OBSTRUCTION

Report of a Case

ARTHUR G. MICHELS, M.D., and THOMAS E. JONES, M.D.
Department of Surgery

THE mesenteric cyst is probably the least common of all abdominal tumors. The rarity of this lesion is indicated by Keesey[1] who reported only 2 cases in 200,000 admissions to a Duluth hospital. The incidence at the Cleveland Clinic during the past fourteen years has been identical: 3 proved cases from a total of 300,000 new patients examined. The first recorded case was found on autopsy in 1507 by Benevieni,[2] and subsequent reports have appeared at intervals, the first successful operation and cyst removal having been performed by Tillaux in 1880.[3]

Numerous theories have been advanced for the origin of such cysts, with many sources implicated, such as hydatid, Meckel's diverticulum, and mesenteric lymphatics. Some writers consider that all cysts are embryonic in origin and initiated by obstruction of existing lymphatic channels or by growth of congenitally misplaced lymphatic tissue which does not communicate with the vascular system. However, the absence of demonstrable inflammation in the mesentery of the usual case makes the theory of lymphatic trunk obstruction a less likely cause. The consensus favors the development of mesenteric cysts from misplaced bits of lymphatic tissue which proliferate and then accumulate fluid because of absence of communication with the remainder of the lymphatic system.

In the usual case the history of a gradually enlarging abdomen is obtained and the most frequent cause for hospital admission is intestinal obstruction. A case of mesenteric cyst complicated by such obstruction is presented.

Case Report

A 7 year old girl was admitted to the hospital with a history of severe intermitten abdominal cramps and occasional vomiting for one week. Seven days before admission the patient had developed sharp recurrent periumbilical pain frequently accompanied by vomiting of gastric contents. The child lay doubled on hands and knees and cried intermittently with pain, rubbing her stomach while in distress. Between spasms she appeared moderately comfortable until the onset of another cramp which usually appeared every half hour to an hour. She had been hospitalized elsewhere for three days previous to admission and intravenous fluid had been prescribed while roentgen studies were made. The patient had had several formed stools the week previously, the most recent on the day before admission to the Cleveland Clinic.

Past history disclosed that approximately one year prior to admission the girl had experienced a somewhat similar attack of pain for which an appendectomy had been performed. At operation an "acute ileitis" was observed, involving a number of plaques and

enlarged mesenteric lymph glands. Since convalescence the patient had had several attacks of similar pain which had persisted two to three days, in each case attributed to dietary indiscretion.

Physical examination disclosed a well-developed, moderately well-nourished but fatigued girl who appeared acutely ill, frequently remained motionless, face down, with hands and knees doubled, and who cried intermittently with pain while massaging her abdomen. The pain lasted three to five minutes only to reappear. Her blood pressure was 110/70, temperature 99 F., pulse 120, and respiration 20. The tongue was moist and of good color; the skin was clear and dry, with lung fields normal to auscultation and percussion. The heart rhythm was regular, with no enlargement or murmurs. The child's abdomen was soft and non-tender when not experiencing abdominal pain. No distinct masses were evident and investigation for bowel sounds proved unsatisfactory during cramps. Further examination disclosed a well-healed right lower quadrant McBurney scar and absence of hernia or visible peristalsis. Rectal examination revealed a firm movable left lower quadrant mass which was believed to be inspissated barium. The remainder of the examination did not reveal any abnormalities.

Laboratory examination disclosed the hemoglobin to be 12 Gm. while the white cell count was 9800. Urinalysis showed a specific gravity of 1.026 and was negative for sugar and albumin, although the sediment contained occasional white cells. The protein totalled 7.3 gr. per 100 cc.

Review of films taken elsewhere and admission flat film of the abdomen demonstrated barium in the cecum, ascending, transverse, and descending colon. There was a faint concentration of barium in the duodenum and a greatly dilated second and third portions of the duodenum with obstruction demonstrated near the ligament of Treitz, the exact cause undetermined (figs. 1a and b).

The patient was placed on gastric suction with a small Miller-Abbott tube, and fluids were given by clysis and vein to restore the electrolyte balance. Chlorides rose from a low of 379 mg. per cent on the second hospital day to 511 mg. per cent on the third hospital day, while the carbon dioxide combining power rose from 38.5 mg. per 100 cc. on the second hospital day to 55.7 mg. per 100 cc. on the third hospital day. The colon was gradually emptied of barium by repeated oil retention and saline enemas. With decompression of the stomach and duodenum the abdominal cramps subsided in two days and the patient began to improve progressively. Temperature varied during the preoperative period between 98.6 F. and 99.8 F.

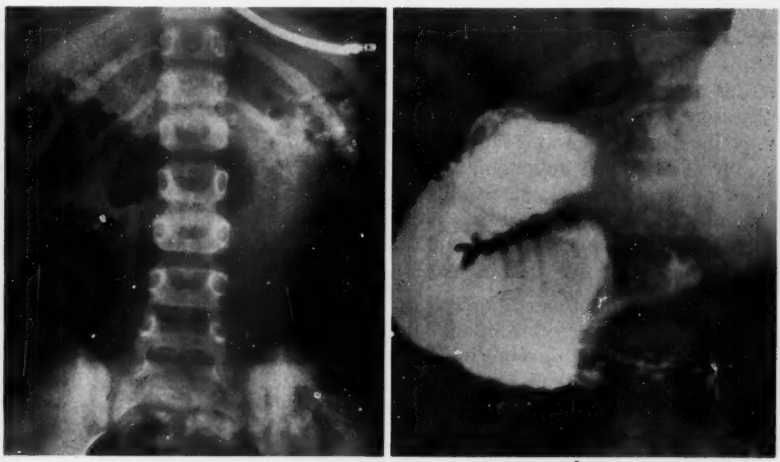
On the sixth hospital day she was taken to surgery and through a midline upper abdominal incision the abdominal cavity was explored. The small bowel immediately presented an unusual configuration and further exploration disclosed a dumbbell-shaped cyst approximately 8 by 10 cm. lying along the mesenteric border of the jejunum 5 inches distal to the ligament of Treitz. The heavy liquid-filled cyst had acted as a pendulum swinging the entire small bowel in a clockwise rotation with the base of the congenitally short mesentery acting as the pivot point. With rotation of a full turn the jejunum had become obstructed just distal to the ligament of Treitz. The obstruction was apparently not always complete and the degree depended upon the tightness with which the small bowel was twisted about the mesenteric pedicle. Concomitant with the findings was severe mesenteric adenitis of the small bowel but no evidence of regional ileitis as previously reported. By rotating the mass of small bowel counter clockwise a full turn the volvulus was reduced and the mesenteric cyst then dissected free from the mesentery without impairment of the adjacent small bowel blood supply. During the dissection the cyst was fractured and approximately 300 cc. of clear yellow fluid was removed by suction. Following cyst removal the rent in the mesentery of the jejunum was closed and the abdominal wall sutured in layers.

The postoperative course was uneventful and afebrile. The patient passed a formed stool on the fourth postoperative day and was discharged asymptomatic on the seventh postoperative day.

The pathologic diagnosis was a simple mesenteric cyst, which on microscopic examination, showed highly vascular fibrous tissue and smooth muscle covered by thin flattened well-separated cells.

Discussion

The contents of mesenteric cysts denote the accidents that have befallen the cyst and which infrequently have any bearing on the etiology. The fluid within the cyst commonly is of two sorts: colorless lymphatic or serous fluid found in approximately 36 per cent, with the second major group containing chylous fluid which has the appearance and consistency of yellow-white milk (35 per cent). Occasionally other contents are present such as blood, sebaceous material, dermoid contents or malignant cells. The typical serous fluid reaction is alkaline, with a specific reaction of 1.015-17 and some cell debris; should



a. *b.*

FIG. 1. (a) Abdominal film demonstrating gas in distended duodenum. Tube in stomach. (b) Barium outlining distended duodenum and stomach with point of obstruction in distal portion of duodenum.

lymphatics be draining from the intestinal tract to the cyst region the fluid may contain a high fat percentage. Chemical analysis of the cyst fluids discloses concentrations of sodium, chlorides, nitrogen, protein, fat and cholesterol which approximate their respective concentrations in plasma.

Mesenteric cysts may occur in any part of the mesentery of the small or large bowel but are most commonly found in the mesentery of the ileum (31 per cent). Ladd and Gross[4] found that in only 2 of their 8 cases the cyst involved the transverse mesocolon and mesosigmoid respectively. Of the 129 cases reviewed by Warfield[5] approximately 48 per cent were in the small bowel mesentery, 50 per cent in the large bowel mesentery and 2 per cent in the mesoappendix or gastrohepatic mesentery.

The cysts rarely produce dysfunction when quite small, and usually yield symptoms justifying operation only after reaching a large size, some large enough to fill the entire abdomen. The majority are unilocular, and a few

multicystic with ducts connecting two or more chambers. In Warfield's series[5] 50 per cent were unilocular while the other half were composed of two or more compartments. The cysts may be situated anywhere between the peritoneal leaves of the mesentery from the mesenteric base to the enteric border. The thin cyst wall consists chiefly of connective tissue with no demonstrable muscular coat, and is lined with simple columnar or flattened epithelium. The cyst may project from either or both surfaces of the mesentery to form a dumbbell or saddle-shaped structure which, as it increases in size, may obstruct the enclosed loop of the intestine by pressure or kinking.

Many descriptions in the literature confuse true mesenteric (lymphatic) cysts with enteric cysts, which are actually duplications. Ladd and Gross[4] explain that these two lesions are pathologically different and require different forms of treatment. The duplication is a thick-walled structure which has a serous coat, two layers of smooth muscle, and a mucous membrane lining. The removal of this type of structure intimately associated with the intestine may involve considerable adjacent bowel trauma and injury to the blood supply of both the duplication and segment of the intestine, as they are nourished by the same vessels. In contrast, the thin mesenteric cyst wall has no muscular coat or mucosal lining and can be dissected free from the bowel and mesentery by following the lines of cleavage without injuring the bowel or its blood supply, as illustrated in the foregoing case report.

There are no pathognomonic signs of this disease. Symptoms of mesenteric cysts are rarely detected in infancy but are more usual the first decade of life. Intestinal obstruction occurs in approximately one third of the cases and is often produced by the progressive narrowing or kinking of the bowel from the mechanical action of the enlarging cyst. Complications such as hemorrhage into the cyst, rupture of the cyst into the peritoneal cavity, torsion of the cyst or impaction into the pelvis, have all been reported. Several observations suggest a diagnosis of mesenteric cyst; a palpable abdominal mass with great mobility in the transverse plane, fluid wave in the mass, or a soft tissue gasless mass on x-ray studies. If a mass is demonstrated by roentgenograms and lies in front of the intestine the diagnosis of omental cyst should be considered.

The treatment is entirely surgical with emphasis on the treatment of the complications. The technical procedures of cyst removal are not difficult and recurrences infrequent. The procedure of choice is enucleation or dissection of the cyst out from the mesentery peeling away the peritoneal leaves from the underlying mass and displacing the important blood vessels from the line of dissection. This procedure involves the lowest mortality (9 per cent). Other procedures have been used with less degree of success such as resection of the cyst and adjacent portion of the intestine with primary side-to-side anastomosis (mortality 27 per cent), and marsupialization of the cyst (mortality 16 per cent). Of the 129 cases reviewed by Warfield[5] the 18 per cent fatalities were equally divided by sex; 52 per cent in patients of 5 years or younger; 23 per cent from five to thirty years of age and 25 per cent of the patients incurring fatalities were over 30 years of age.

Summary

A case of mesenteric cyst of the jejunum was characterized by intermittent obstructive symptoms for more than one year and followed by signs of complete intestinal obstruction. At operation a dumbbell-shaped cyst was disclosed which had produced a volvulus of the entire small bowel and obstruction just distal to the ligament of Treitz. Following removal of the cyst and reduction of the volvulus the patient attained an uneventful recovery and was discharged asymptomatic.

References

1. Keesey, W. E.: Cysts of mesentery; review of literature and report of case. Illinois M. J. **73**:333-336 (April) 1938.
2. Benevieni, cited by Warfield, J. O., Jr.[5]
3. Tillaux, cited by Warfield, J. O., Jr.[5]
4. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood (Philadelphia: W. B. Saunders Company, 1941).
5. Warfield, J. O., Jr.: Study of mesenteric cysts with report of 2 recent cases. Ann. Surg. **96**:329-339 (Sept.) 1932.

IDIOPATHIC STEATORRHEA

Report of Thirty Cases

CHARLES H. BROWN, M.D.
Department of Gastroenterology

IDIOPATHIC steatorrhea or sprue is a condition in which many of the nutritional principles, complications and therapeutic characteristics are equally applicable to other disorders producing malnutrition and steatorrhea.

Sprue or idiopathic steatorrhea may be defined as a chronic deficiency disease with a definite tendency to remission and relapse, characterized by glossitis, stomatitis, anorexia, gastrointestinal symptoms, by the passage of large frothy, foul-smelling stools, by great muscular wasting, nervous symptoms, decalcification, and in adults by a macrocytic hyperchromic anemia.

The etiology of steatorrhea or fatty stool may be classified as follows:

1. Lack of secretions
   a. Lack of bile (calculi, carcinoma, etc.)
   b. Lack of pancreatic secretions (calculi, chronic pancreatitis, neoplasm, cystic fibrosis)
2. "Secondary" sprue
   a. Postgastrectomy
   b. Gastrocolic and jejunocolic fistulae
   c. Mesenteric lymph node disease (tuberculous, neoplasm)
   d. Lymphatic obstruction
   e. Intestinal lipodystrophy (Whipple's disease)
   f. Regional enteritis
   g. Sequelae of protozoan and bacillary dysenteries
   h. Amyloidosis of small intestine
3. "Primary" sprue
   a. Tropical sprue
   b. Non-tropical sprue
   c. Coeliac disease

The recent war stimulated medical interest in these diseases. One writer[1] observed more than 1000 cases of sprue in a prison camp. Also the introduction of folic acid and the work by Spies and his associates[2] aroused attention concerning sprue and allied conditions.

The **etiology** of sprue is still not understood. It was originally thought to be due to intestinal parasites, particularly the Monilia group of organisms; however, it is generally agreed that the finding of parasites in the stool is merely coincidental in these patients.

In sprue there is some change in the mucous membrane of the small bowel that results in impaired absorption of fat. There may be a defect in the phosphorylation of carbohydrates and fats; the latter are normally split in sprue

patients by the digestive juices but not absorbed. This lack of absorption results in the entire clinical picture:

1. Increased fat in the stool causes diarrhea.
2. Lack of absorption of the intrinsic factor causes macrocytic anemia.
3. Lack of absorption of calcium causes osteoporosis, dwarfism, skeletal changes and tetany.
4. Lack of absorption of vitamin D acts synergistically with the lack of calcium and causes similar changes.
5. Lack of absorption of vitamin A causes some of the skin changes and occasionally lens opacities.
6. Lack of vitamin K absorption may cause a hemorrhagic picture.
7. Lack of absorption of vitamin B components causes glossitis and stomatitis.

The primary defect in sprue—impaired fat absorption—is not corrected by specific therapy (folic acid or liver extract). Vitamin A tolerance curves remain flat despite treatment,[3] indicating that the primary defect is still present.

Pathologically, little is found. Many workers have failed to discover significant changes in the intestines when an autopsy was performed immediately. The intestines may be thin and atrophic; the fat deposits of the body are depleted and there is generalized atrophy of all internal organs. Castle[4] has shown that the liver in sprue patients lacks the erythrocyte maturing factor. Spies[2] has described distinct shortening and blunting of the villi, accompanied by an increase in the number of plasma cells in the tunica propria in about one half of autopsied sprue patients. Bone marrow changes are not distinguishable from those accompanying pernicious anemia.

The **clinical picture** of sprue is often confusing. The onset is usually insidious with a history of a previous debilitating illness such as malaria or dysentery or with a poor nutritional history. Gastrointestinal symptoms of anorexia, flatulence, epigastric fullness appear. The dyspepsia, anorexia, and abdominal discomfort increase until the patient becomes a chronic dyspeptic, further limiting his dietary intake. The tongue and mouth become sore, with aphthae developing and with the tongue assuming a bald beefy red appearance. The patient passes semi-solid or fluid stools that are frequently foul smelling, or occasionally one large stool a day. In addition he loses considerable weight. Ashford[5] stated that, "Sprue literally dissects its victim." The skin develops a dirty brownish yellow color with patchy pigmentation of the forehead and malar eminences. Unlike Addison's disease there is no pigmentation of the mucous membrane. Edema, due to the low dietary protein intake, may develop; this was common in the sprue seen in prison camps in the recent war. There may be a central nervous system irritability with vague aches and pains, paresthesias of the hands and feet. Subacute combined degeneration occurs rarely.

Complications of sprue may be the primary complaint of the patient, particularly in northern climates. There may be lens opacities due to vitamin A deficiency, a bleeding tendency because of lack of vitamin K, tetany due to a

low serum calcium, osteoporosis in adults and dwarfism and rickets attributable to lack of absorption of vitamin D and a negative calcium balance. Backache caused by osteoporosis or bleeding may hasten a consultation.

In the past ten years, 30 cases of sprue have been observed at the Cleveland Clinic. The complaints of these patients are listed in Table 1.

TABLE 1.

Symptoms in Sprue Patients at the Cleveland Clinic

Symptom	No. of Cases (30)
Diarrhea	27
Loss of over 20 pounds	21
Sore tongue	12
Flatulence	11
Edema	8
Osteoporosis (symptoms from)	6
Tetany	5
Anorexia	5
Hemorrhage	3
Pernicious anemia	1

The duration of symptoms in our cases was less than one year in 8 cases, one to five years in 16 cases and over five years in 6 cases.

In our experience many patients presented themselves with symptoms of complications of sprue, rather than with the usual cardinal symptoms of the condition. Frequently it is only by direct questioning that the history of diarrhea or a sore tongue may be elicited.

One patient complained of "pernicious anemia." However, free hydrochloric acid was present on gastric analysis. Laboratory studies and small bowel roentgenograms confirmed the diagnosis of sprue.

Tetany was the primary complaint in 2 cases. On further questioning it developed that both patients had diarrhea. One of them was admitted to the hospital and a serum calcium of 6.8 mg. per 100 ml. was found. Under treatment the calcium increased, tetany disappeared, he gained weight and the diarrhea stopped. About six months later treatment was discontinued. The diarrhea returned, the patient lost weight, and shortly thereafter was readmitted to the hospital because of tetany. Once again he responded promptly to the treatment.

Two other patients were observed primarily because of a bleeding tendency. One patient, previously reported by Collins and Hoffmann,[6] had hematuria and hemoptysis. The second patient had subcutaneous hemorrhages. Both responded quickly to the treatment of the underlying sprue.

Two other patients complained of edema caused by low serum proteins associated with sprue.

Another patient complained of pain in the back. Roentgenograms of the back revealed severe osteoporosis and collapse of three vertebrae. Seven years

previously he had had a gastro-enterostomy, subsequently developing a diarrhea that had never been troublesome. Gastrointestinal x-ray examination revealed a gastrocolic fistula. This is an example of "secondary" sprue. Three other such cases due to an inadvertent gastro-ileostomy have been reported by Brown, Colvert and Brush.[7]

Consequently it is evident that many sprue patients do not have the classical picture of sprue but complain of complications of this disorder. This may be because, with the lower incidence of the disease in this climate as compared to the tropics, we are less aware of its possible existence until a complication of the condition arises. Consequently, sprue should be considered in any patient with steatorrhea, loss of weight, unexplained edema, macrocytic anemia, tetany or osteoporosis.

The **laboratory examinations** in a patient suspected of having sprue are frequently helpful. On gastric analysis 40 per cent are shown to have achlorhydria, while others disclose hypochlorhydria. Gastroscopically 40 per cent show an atrophic gastritis. In children the blood picture is usually that of a hypochromia anemia, while in the fully developed adult case the blood picture is that of a hyperchromic, macrocytic anemia. There is more than 30 per cent fat in the stool, the fat being largely split (77 per cent). A rough estimation of the split fat in the stool can be obtained by staining with sudan 3. There is a flat oral glucose tolerance curve. In 65 cases of sprue at Duke reported by Hanes[8] only 5 showed a rise of more than 40 mg. per 100 ml. after 1.5 Gm. of glucose per kilo body weight had been given orally. Serum cholesterol and serum proteins may remain low. Both serum calcium and serum phosphorus are low, differentiating the condition from hypoparathyroidism. Vitamin A tolerance curves are flat.

The laboratory observations in our cases are presented in Table 2.

Roentgen-ray examination of the bones of a patient with sprue may show osteoporosis in adults and rickets and deformities in children. The colon may be large and atonic. Frequently x-ray examination of the small bowel is practically diagnostic. With sprue there is obliteration of the herringbone markings due to the vulvulae conniventes, moulage formation or smoothing of the contours of the lumen, dilatation of the small bowel, clumping of barium, and hypomotility. Rarely will other conditions such as pylorospasm and pyloric lesions (Glass[9]) cause a similar bowel picture. Typical roentgenograms are presented in figures 1a and b.

The **diagnosis** of sprue is based on the history, physical, laboratory, and roentgen-ray examinations. A history of steatorrhea, diarrhea, loss of weight, gastro-intestinal symptoms of flatulence, epigastric fullness, and anorexia is suggestive. On physical examination there may be glossitis, stomatitis, pigmentation and emaciation. Laboratory examinations reveal a flat oral glucose tolerance curve, low serum calcium and phosphorus, a macrocytic anemia in adults, a hypochromic anemia in children, and a high split fat in the stool, Roentgenograms of the small bowel may show dilatation and hypomotility.

TABLE 2

Laboratory Observations in 30 Cases of Sprue

Observations	No. of Cases
Anemia	24
Macrocytic	18
Stool—increased fatty acid crystals	29
Serum calcium—below 9 mg./100 ml.	18
Not done	5
Serum phosphorus—below 3 mg./100 ml.	11
Not done	14
Ewald—normal	11
Hypochlorhydria	12
Hyperchlorhydria	2
Not done	5
Serum proteins—below 6 Gm./100 ml.	14
Not done	13
Oral glucose tolerance—flat	9
Normal	2
Not done	19
Prothrombin—low	3
Gastroscopic—normal	2
Atrophic gastritis	1

In the **differential diagnosis,** other causes of steatorrhea are differentiated from sprue by the presence of meat fibers or high unsplit fat and increased nitrogen in the stool, a normal oral glucose tolerance curve, normal serum calcium, and normal small bowel motility studies. Further investigation will often reveal pancreatic disease with a lack of pancreatic enzymes, a gastrocolic or gastroileal fistula as the cause of the steatorrhea.

Pernicious anemia can be differentiated from sprue by the flat glucose tolerance test, the frequent presence of hydrochloric acid on gastric analysis, increased split fat in the stool, and the small bowel changes that are associated with sprue rather than pernicious anemia.

Addison's disease may be differentiated by the pigmentation of the mucous membrane, non-existent in sprue, by the normal glucose tolerance curve and by the study of the stool.

Other causes of diarrhea must of course be distinguished from sprue, and this can be done by the laboratory observations of a macrocytic anemia, high split fat in the stool, and by the typical x-ray findings in patients with sprue.

In **treatment** the diet must be fluid at first, high in protein and carbohydrate. Frequent small feedings should be given. The diet should be increased until the patient is receiving 150 Gm. of protein and 300 Gm. of carbohydrate a day. The fat content of the diet should be kept low and increased as tolerated. Two cubic centimeters of liver extract parenterally should be prescribed every

day. Spies[2] has shown that it makes little difference whether refined or crude liver extract is given to these patients.

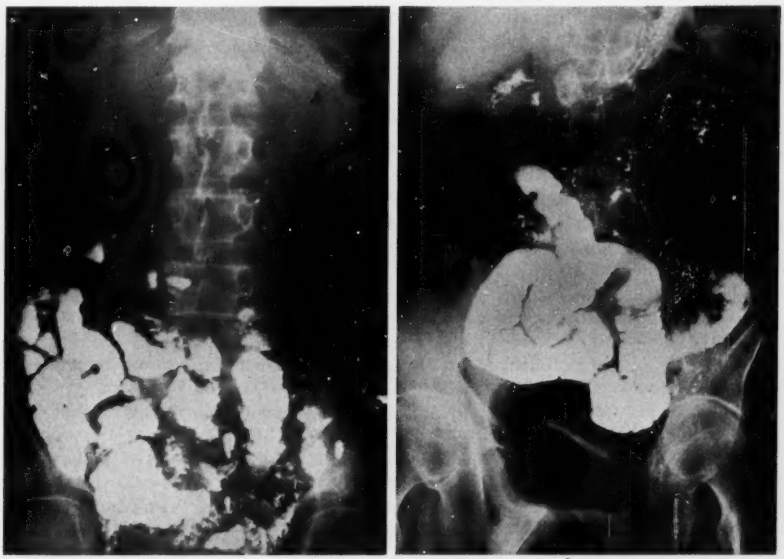
Folic acid has been proved to be specific at least for the anemia of sprue.[2] Frequently the diarrhea and other symptoms disappear when the patient is given folic acid as the only therapeutic measure,[2] although this is not recommended. Initially, the patient should get from 10 to 20 mg. of folic acid orally each day. As a maintenance dose, he should receive 2.5 to 5.0 mg. daily.

Two cubic centimeters of vitamin B complex given daily, parenterally, is helpful in treating these patients. Later, oral doses of vitamin B complex may be prescribed, either in the form of Brewer's yeast or in high potency capsules.

Because of the negative calcium balance, these patients should receive extra calcium. This may be given in the form of calcium lactate, 15 gr. three times a day.

Vitamins A and D should be prescribed because of the impaired absorption of fat substances, preferably one c.c. daily of viosterol or halibut oil. Vitamin K may be used if there is any decrease in the prothrombin time.

Mecholyl was used successfully in one patient in an effort to increase the tone of the small intestine and cause better absorption.



a. *b.*

FIG. 1 (a) Small intestinal x-ray in patient with sprue showing dilatation, moulage, and segmentation. (b) Small intestinal x-ray in patient with sprue showing dilatation and moulage of the intestinal wall.

If, on the described program, the patient is still unable to gain because of impaired fat absorption, Tween 80 or polyoxyethylene sorbitan monooleate may be used in a dose of 1.5 Gm. before each meal. This drug is an emulsifying agent and breaks the fat into smaller globules probably by lowering the surface tension. Jones et al.[3] have described its use in cases of sprue of both the primary and secondary types.

What are the **effects of treatment?** In the usual case of sprue the symptoms promptly disappear, the oral glucose tolerance and the blood count quickly become normal. There may be a fairly rapid gain of weight. Although clinically the patient may improve, the flat vitamin A tolerance curve persists. This indicates that the basic difficulty—fat absorption in the small intestine—is not corrected by treatment with folic acid or liver extract.

In our group of cases improvement was rapid in all but 4. One patient received testosterone to improve nitrogen metabolism, and responded promptly to this addition to his therapeutic program. Two others, originally diagnosed as sprue patients, were subsequently found to have tuberculosis which proved fatal. Their original conditions were undoubtedly tabes mesenterica. This shows the importance of obtaining a chest roentgenogram in every patient with sprue. The fourth patient was reported to have died of cancer, the site of the growth not having been disclosed.

Because of the fact that irreversible damage may occur, it is important that patients be treated intensively with all of the measures outlined.

References

1. Stefanini, M.:Hypoproteinemia and edema in course of tropical sprue. Gastroenterology **11**:50-55 (July) 1948.
2. Suarez, R., Spies, T. D., and Suarez, R. M., Jr.: Use of folic acid in sprue. Ann. Int. Med. **30**:643-677 (May) 1947.
3. Jones, C. M., Culver, P. J., Drummey, G. D., and Ryan, A. E.: Modification of fat absorption in digestive tract by use of an emulsifying agent. Ann. Int. Med. **29**:1-10 (July) 1948.
4. Castle, W. B., Rhoads, C. P., Lawson, H. A., and Payne, G. C.: Etiology and treatment of sprue. Ann. Int. Med. **56**:627-699 (Oct.) 1935.
5. Ashford, B. K.: Observations on the conception that sprue is a mycosis superimposed upon a state of deficiency in essential food elements. Am. J. Trop. Med. **2**:139-150. (March) 1922.
6. Collins, E. N., and Hoffman, A. D.: Hemoptysis and hematuria in sprue; importance of vitamin K metabolism. Cleveland Clin. Quart. **10**:105-111 (Oct.) 1943.
7. Brown, C. H., Colvert, J. R., and Brush, B. E.: Gastro-ileostomy, rare surgical error: symptoms and x-ray findings. Gastroenterology. **8**:71-81 (Jan.) 1947.
8. Hanes, F. M.: Sprue. Oxford Medicine **5**: (part 2) 631-652, 1942. (New York: Oxford University Press).
9. Glass, W. H.: Non-vitaminic factors involved in production of "small intestinal deficiency pattern." Gastroenterology. **10**:660-666 (Apr.) 1948.

BUNTS LECTURES

The Frank E. Bunts Educational Institute has scheduled the following Bunts lectures for 1949. These lectures will be held in the Founders and Staff Room of the Cleveland Clinic at 8:15 p.m. Visitors are cordially invited.

January 17, 1949—Dr. Arthur W. Allen
Venous Thrombosis and Pulmonary Embolism.

February 7, 1949—Dr. Ernst von Lauda
Differential Diagnosis of Various Types of Liver Cirrhosis.

March 21, 1949—Dr. Thomas M. Rivers
Viruses and Their Relationship to Host Cells.

RETIRING

On January 1, 1949, Dr. Russell L. Haden is retiring as Chief of Staff of Medicine. Dr. Haden will, however, continue his association with the Clinic as a member of the Foundation and Bunts Institute, and as Consultant in Medicine and Research, and as Professor Emeritus of Medicine in the Institute. Also retiring on January 1, 1949, is Dr. Howard Dittrick, who has been with the Clinic since 1944. On the same day Dr. A. Carlton Ernstene, who has been head of the Section on Cardiovascular Disease for many years, will become Chief of Staff of Medicine.

APPOINTMENT

Dr. Leonard L. Lovshin has been made a member of the staff of the Division of Medicine. Dr. Lovshin graduated from the University of Wisconsin in 1935 and from the University of Wisconsin Medical School in 1939. Following a two year internship at the Philadelphia General Hospital, he was a Fellow at the Mayo Clinic from 1941 to 1942. After serving in the U. S. Army for four years, he returned to the Mayo Clinic for two additional years as a Fellow in the Division of Internal Medicine.

DECEASED

Justin Miner Waugh, M.D.
1872-1948

Dr. Waugh, who died on November 24, 1948, was one of the original members of the Cleveland Clinic staff serving from 1921 until his retirement in 1944. He was the first head of the Department of Otolaryngology. Active participation in and contribution to his special field of medicine brought him wide recognition and respect. He was elected to many medical societies including the American Laryngological, Rhinological and Otological Society, the American Broncho-esophagological Association, the American Academy of Ophthalmology and Otolaryngology, and the American College of Surgeons.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

A continuation course will be presented on
Thursday, Friday, and Saturday, March 17, 18, and 19, 1949

DIABETES

Tentative Program

Thursday, March 17, 1949

8:00-9:00 a.m.	Registration	
9:00 a.m.	Physiologic Properties of Insulin	E. Perry McCullagh, M.D.
9:30 a.m.	Diagnosis of Diabetes	R. W. Schneider, M.D.
10:00 a.m.	Recent Developments in Experimental Diabetes	Arnold Lazarow, M.D.*
10:45 a.m.	Selection of Diet	R. W. Schneider, M.D.
11:15 a.m.	Menus for Diabetes	Marjorie R. Curry, B.S.
11:45 a.m.	Demonstration of Patients	
12:15 p.m.	Luncheon	
1:15 p.m.	Pathology of Diabetes	J. B. Hazard, M.D.
1:45 p.m.	Choice of Insulin Preparation	E. Perry McCullagh, M.D.
2:15 p.m.	Insulin Mixtures	Irving Sparks, M.D.*
3:00 p.m.	Complications Resulting from Insulin	A. Gold, M.D.
3:30 p.m.	Pancreatic Disorders	C. H. Brown, M.D.
3:50 p.m.	Disturbances of Glucose Metabolism in Liver Diseases	H. R. Rossmiller, M.D.
4:10 p.m.	Diabetic Coma	E. E. Beard, M.D.*

GUEST SPEAKER

8:15 p.m.	Modern Trends in Diabetes	Henry T. Ricketts, M.D. Associate Professor of Medicine, University of Chicago

Friday, March 18, 1949

9:00 a.m.	Diabetes in Pregnancy	Max Miller, M.D.*
9:30 a.m.	Diabetes in Childhood	H. J. John, M.D.*
10:00 a.m.	Hyperinsulinism	R.W. Schneider, M.D.
10:45 a.m.	Diabetic Retinopathy	R. J. Kennedy, M.D.
11:15 a.m.	Neurological Phases of Diabetes	L. J. Karnosh, M.D.
11:45 a.m.	Demonstration of Patients	
12:15 p.m.	Luncheon	
1:15 p.m.	Renal Glycosuria	A. C. Corcoran, M.D.
1:45 p.m.	The Kidney and Diabetes	R. D. Taylor, M.D.
2:15 p.m.	Dermatologic Problems Encountered in Diabetes	E. W. Netherton, M.D.
3:00 p.m.	Coronary Heart Disease in Diabetes	A. C. Ernstene, M.D.
3:30 p.m.	Gangrene: Indications for Surgery	J. A. Dickson, M.D.
4:00 p.m.	Pre and Postoperative Management of the Diabetic Patient	E. Perry McCullagh, M.D.
5:00 p.m.	Cocktail Hour, Wade Park Manor	

Saturday, March 19, 1949

9:00 a.m. . . . . Vascular Complications of Diabetes . . . . . FAY LEFEVRE, M.D.

GUEST SPEAKERS

9:30 a.m. . . . . Public Health Aspects of Diabetes . . . H. L. C. WILKERSON, M.D.
U. S. Public Health Service

10:00 a.m. . . . . Role of Pituitary and Adrenal Glands in Diabetes
J. S. L. BROWNE, M.D.
Professor of Medicine, McGill University

10:45 a.m. . . . . Panel Discussion: Drs. Browne, McCullagh, Schneider, Wilkerson and LeFevre with Dr. Jordan as Moderator.

*By Invitation.

Questions pertaining to diabetes may be submitted in writing for the panel discussion. A "Question Box" during the first two days of the course will be available for the convenience of those wishing to present questions to the members of the panel.

REGISTRATION BLANK

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE
Cleveland Clinic Building
2020 East Ninety-third Street
Cleveland 6, Ohio

. . . . . , 1949

Please register me for the course on "Diabetes" which is to be given March 17, 18, and 19, 1949.

I am enclosing check for $5.00 and the remainder of the fee, $10.00, will be paid on Registration, March 17.

NOTE: Checks should be made payable to the Frank E. Bunts Institute. Mail registration blank and check to Dr. Edwin P. Jordan, Cleveland Clinic Building, 2020 East Ninety-third Street, Cleveland 6, Ohio.

Name . . . . . .

Address . . . . . .

Medical School and
date of graduation . . . . . .

This course is open only to graduates of approved medical schools. Registration will be limited to the number of physicians who can be adequately accommodated.

MEDICAL LIBRARY
HISTORICAL BUILDING
DES MOINES, IOWA

GLAUCOMA

ROSCOE J. KENNEDY, M.D.
Department of Ophthalmology

GLAUCOMA which involves an increase in the intraocular pressure is one of the most serious problems in ophthalmology. This increase in pressure is generally due to a disturbance between the production and the absorption of the aqueous humor, although many factors enter into this. Since the normal pressure varies from 15 to 30 mm. of mercury anything higher is considered abnormal.

For convenience glaucoma is usually divided into several types:

1. Primary including (a) acute congestive, (b) chronic simple, and (c) absolute.
2. Secondary.
3. Congenital (buphthalmos and hydrophthalmos).

Sudden loss of sight, severe and excruciating pain, and possibly associated vomiting are characteristic for acute congestive glaucoma. Usually the patient is not aware of any prodromal signs, although these may be present, such as halos about lights and transient attacks of mild pain. One eye only is commonly involved although there is a tendency for the other eye to become affected later. Examination may reveal some edema of the eyelid and there is usually congestion of the bulbar conjunctiva. The cornea is steamy and the anterior chamber is almost obliterated. The pupil is mildly dilated and fixed. Usually the fundus cannot be seen. The intraocular pressure is elevated, often measuring as high as 80 to 90 mm. of mercury.

The patient is frequently in such pain that an examination is difficult, but vision may be reduced to light perception. Visual field changes usually cannot be obtained due to the severe pain from which the patient is suffering. Treatment consists of the prompt use of miotics, such as 1 per cent eserine, D.F.P. (0.1 per cent). Morphine should be prescribed for pain as needed. If the attack does not subside within a few hours with the use of miotics, surgical intervention is indicated. It is generally believed that if the pressure is not reduced within forty-eight hours sight is irreparably damaged, and therefore surgery should not be postponed. The operation of choice is basal iridectomy, although there is a growing tendency to prefer iridencleisis if the attack is prolonged more than twelve hours. The prognosis in such cases is good if the intraocular tension is reduced to normal within forty-eight to seventy-two hours.

The following illustrates a typical case of acute congestive glaucoma.

Case 1. A man aged 66 was first seen in May 1945, at which time his visual acuity was 6/30 in each eye. Visual fields were not diagnostic. Intraocular tension at this time was 25 mm. of mercury (Schiotz) in each eye. On June 4, 1945 the patient developed an increased intraocular pressure in the right eye. On June 7, 1945 a basal iridectomy was performed following which the patient made an uneventful recovery. About one and a half years later

a cataract extraction was done, after which the patient developed an increased intraocular pressure, necessitating enucleation of the right eye on January 29, 1946. He made an uneventful recovery. In February 1947, the visual acuity in the left eye was 6/30 correctable by lenses to 6/6 minus 3. The intraocular pressure was 30 mm. of mercury (Schiotz). The patient was not observed again until December 1947. His left eye had then become blurred after he had attended a movie six days previously, and he complained of pain, nausea and inability to get around by himself. Examination revealed the visual acuity to be reduced to counting fingers at 3 inches. The intraocular tension was 89 mm. of mercury (Schiotz). The diameter of the pupil was 4 to 5 mm. slightly irregular and fixed. The cornea was steamy. A diagnosis of acute congestive glaucoma was made. The intraocular tension could not be brought down by the use of miotics. The patient was admitted to the hospital and a basal iridectomy was performed. The tension has continued to remain normal since that time and when last seen in January 1949, the intraocular tension was 23 mm. of mercury (Schiotz). The visual field had returned to satisfactory proportions as shown in the accompanying diagram (fig. 1).

Chronic simple glaucoma is the most common type of glaucoma observed by the ophthalmologist. It is one of the most insidious of diseases and for that reason is often not detected until late in its course. Although it is said to occur more commonly in the Jewish and Negro races, none is immune. It is slightly more prevalent among women than men and occurs generally after the fourth decade of life. It differs from acute congestive glaucoma in that there is no pain, one reason why it is so often overlooked. The cause of this condition is not known although there are many theories. It is usually bilateral, and one eye may be affected before the other eye. One of the early signs is seeing halos

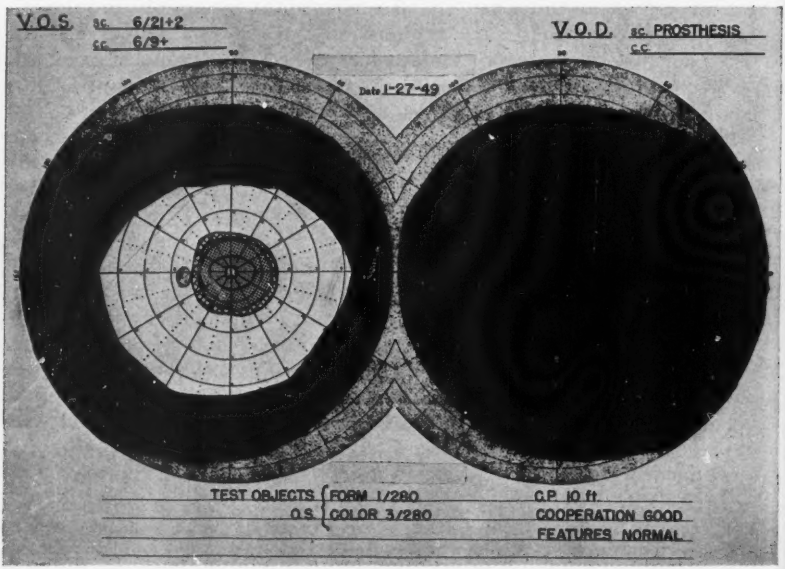


FIG. 1

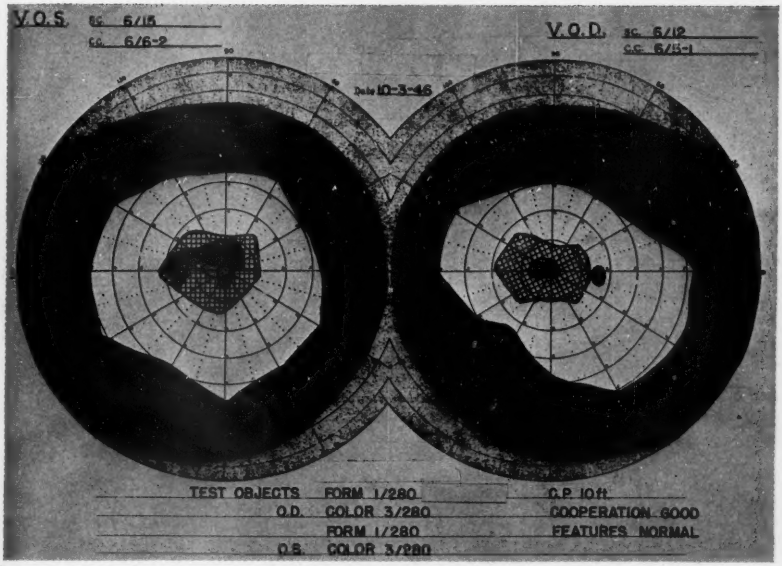


FIG. 2

around lights, but this is often overlooked by the patient. If he is asked concerning "halos," however, he will reply in the affirmative.

Clinically the eye appears relatively normal as far as inflammation is concerned. The cornea and sclera are clear. There is usually a shallow anterior chamber although it may be normal. The pupil may be mildly dilated. The common fundus picture in an early case is that of a clear vitreous and a relatively normal disk. In the later stages, there is cupping of the disk and associated optic atrophy. The vessels can be seen to dip down into the cup as they pass over the edge of the disk, giving them a fish-hook, kinking appearance. The degree of the cupping and the optic atrophy depend upon the time the disease has been present.

The intraocular pressure is elevated, usually somewhere around 40 mm. of mercury, but it may run as high as 60 to 70 mm. of mercury. Central vision is usually maintained extremely late in the disease. Visual fields show characteristic field changes, often the first change being an enlarged blind spot. The enlargement of the blind spot above and below is called Seidel's sign. A continued enlargement of this leads to the Bjerrum scotoma, which increases both above and below the raphe in unequal portions to form the Ronne nasal step. Figs. 2, 3 and 4 show typical visual field changes.

The pressure can often be controlled early in the course of the disease by the use of miotics. Many patients will go for years without loss of vision by their aid and constant use. If the tension cannot be adequately controlled with

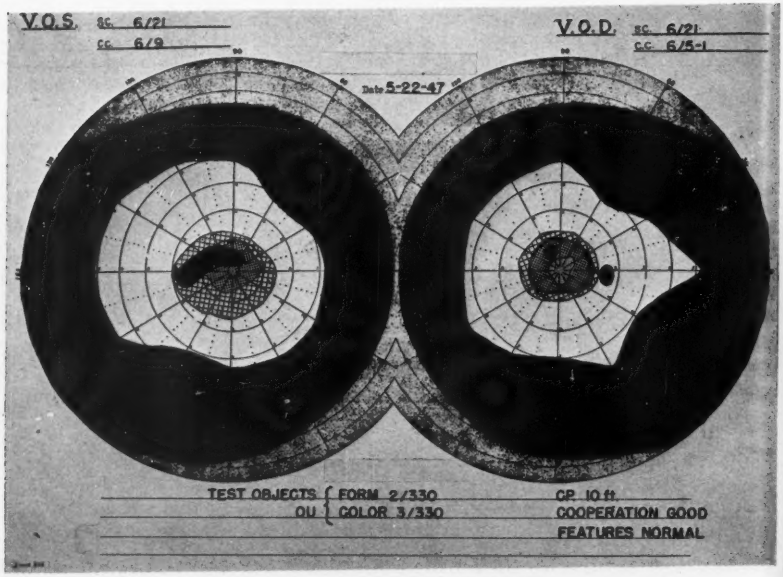

V.O.S.
sc. 6/21
cc. 6/9
V.O.D.
sc. 6/21
cc. 6/5-1
Date 5-22-47
TEST OBJECTS { FORM 2/330
OU { COLOR 3/330
CP. 10 ft.
COOPERATION GOOD
FEATURES NORMAL

FIG. 3

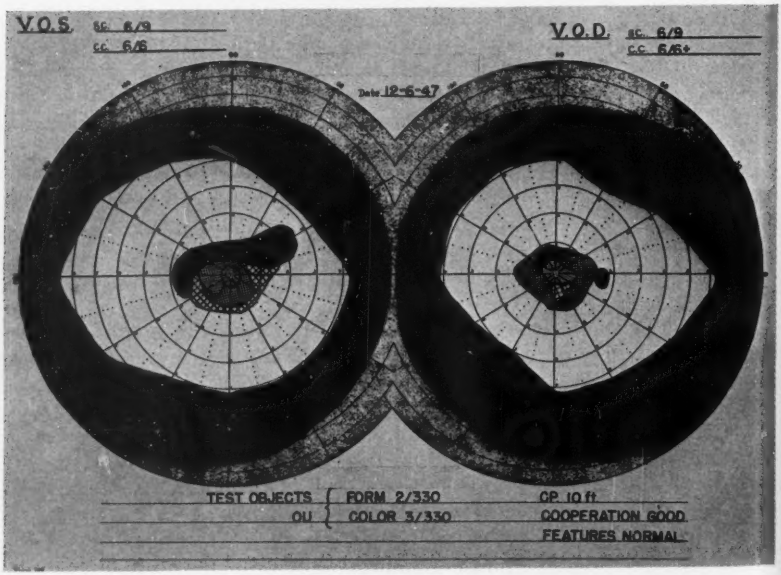

V.O.S.
sc. 6/9
cc. 6/6
V.O.D.
sc. 6/9
cc. 6/6+
Date 12-6-47
TEST OBJECTS { FORM 2/330
OU { COLOR 3/330
CP. 10 ft.
COOPERATION GOOD
FEATURES NORMAL

FIG. 4

miotics or there is a loss of visual field even with normal tension readings surgery is indicated. Some form of fistulizing operation such as an Elliott trephine, is the one of choice. These patients should be seen frequently and repeated visual field tests must be made in order to evaluate the therapy that is in use.

Case 2. A 62 year old woman was first observed in 1928. There was no increase in intraocular pressure until October 1946, at which time there was some slight glaucomatous cupping noted. Intraocular tension measured 30 mm. of mercury in each eye. The patient was placed on 1 per cent pilocarpine three times a day and the tension was adequately controlled. The patient was next seen in May 1947. At this time the intraocular pressure measured 35 mm. of mercury in the right eye and 41 mm. of mercury in the left eye. She was advised to resume the use of 1 per cent pilocarpine which she had discontinued. The drops were to be used in the morning and evening and were later increased to three times a day. When last seen in January 1948, the intraocular pressure was 27 mm. of mercury in the right eye and 30 to 35 mm. of mercury in the left eye. The patient has not been examined since that time. The visual fields shown in figs. 2, 3 and 4 demonstrate the typical changes that are seen in chronic simple glaucoma.

Case 3. A 42 year old man was first examined in February 1949. The patient stated that he first saw colored halos around lights six years previously. A diagnosis of glaucoma had been made two months before examination here at which time the patient was placed on 2 per cent pilocarpine by the referring physician. When seen at the Cleveland Clinic his visual acuity was 6/9 in the right eye and 6/12 plus 3 in the left. The intraocular tension measured 89 mm. of mercury each eye (Schiotz) after the patient had refrained from using eye drops for nine hours. He was instructed to use the drops every three hours and return the following morning, at which time the intraocular pressure was reduced to 23 mm. of mercury each eye. Fundus examination did not reveal cupping although there was slight pallor to each optic disk. Visual field findings were not significant except for enlarged blind spots in each eye (fig. 5).

Absolute glaucoma represents the final phase of primary glaucoma which either had been untreated or treated unsuccessfully. The eye is blind and the tension remains constantly elevated. There is pain and the eye is tender to touch. The cornea is usually cloudy, often showing a bullous keratitis. The entire globe is engorged. Generally the fundus cannot be seen. These patients frequently complain of a constant nagging type of pain, and the feeling of a foreign-body sensation in the eye. Enucleation is the only treatment which can be advised. If the patient refuses, one of several procedures may be tried such as basal iridectomy, Elliott trephine or cyclodiathermy.[1]

Secondary glaucoma represents an increase in intraocular pressure in which the cause is recognized. Some of the causes which may produce this condition are iridocyclitis, uveitis, dislocated lens, swelling of the lens due to rapidly forming cataract, traumatic cataract, intraocular tumors in late stages, retinal detachment, and thrombosis of the central retinal vein. The clinical picture depends on the exciting cause and, for that reason, any patient with an inflammatory lesion of the eye should have the intraocular pressure measured. As many of these inflammatory lesions are treated with mydriatics, it is always important to constantly check the intraocular pressure. If the pressure rises in these cases, one may have to change to miotics in order to control the pressure. In others surgery is indicated. Paracentesis is often sufficient to control the tension and this procedure may be repeated as often as necessary. If paracentesis does not control the pressure then a basal iridectomy should be

done. In the case of a traumatic cataract, the simple washing out of the lens will often suffice to reduce the tension. The following case is typical.

Case 4. A 38 year old man was first seen at the Cleveland Clinic on February 1, 1949. Two weeks previously a wire had punctured his right eye. The roentgenogram was normal for intraocular foreign body. The patient had been referred to the Clinic because of severe pain in the affected eye. Examination of the right eye revealed an intraocular tension of 89 mm. of mercury (Schiotz). The lens was opaque and the anterior chamber was obliterated. The cornea was steamy. The patient had been given miotics for approximately twelve hours. A linear extraction was performed on February 2, after which the intraocular tension dropped to within normal limits. The pupil was kept dilated with atropine. At the time of discharge from the hospital one week following the removal of the lens, the intraocular pressure measured 14 mm. of mercury (Schiotz). The cornea was clear except for a small scar at the point of injury. This case represents a typical secondary glaucoma due to traumatic cataract.

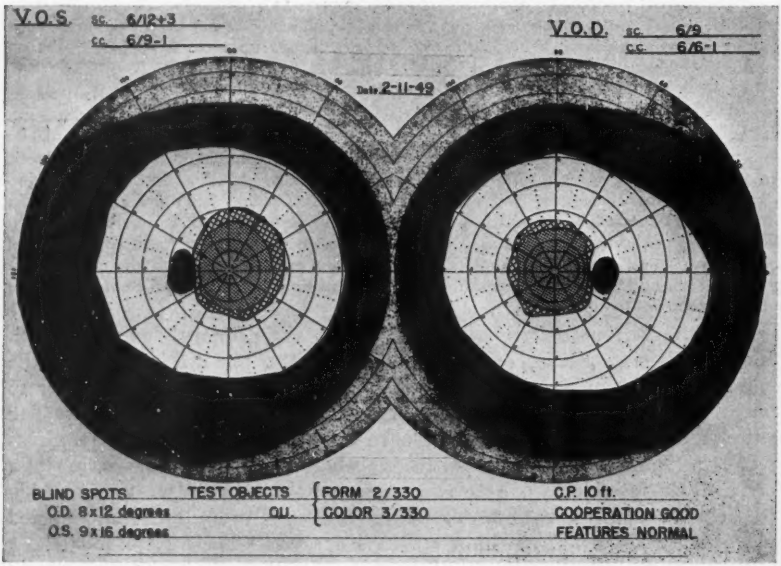


FIG. 5

Congenital glaucoma (buphthalmos, hydrophthalmos) is a condition occurring in infancy in which there is a rise in intraocular pressure. The cornea is larger than normal and as a rule the entire globe is enlarged. The anterior chamber is deep. One can often spot these cases at a glance because of the unusually enlarged appearance of the eye. Pain is uncommon. The condition may be unilateral or bilateral. Cupping of the optic disk may or may not be present, although usually by the time the patient has been seen, there is severe optic atrophy. The tension is elevated often as high as 70 mm. of mercury. In the treatment of these cases, medical therapy is usually of little avail and surgery is required. In the past, trephines and basal iridectomies have been the operation of choice although they have not been too successful. Goniotomy

as described by Barkan[2] seems to offer new hope. The prognosis in these cases is poor, and the end result is usually blindness; however, every attempt should be made to save as much sight as possible and for as long as possible in order that the child may be educated before becoming blind.

Provocative tests in glaucoma are usually not necessary, but there are times when they seem to be indicated, such as when the pressure is not elevated consistently and one is not sure whether or not he is dealing with glaucoma. The following are three of the commonly used tests:

(1) The dark room test can be carried out in the physician's office. The tension is first measured following which the patient is placed in a dark room for one to two hours. Following this, the tension is again rechecked in as subdued light as possible. If there is glaucoma present, the tension will usually rise anywhere from 5 to 15 mm. of mercury.

(2) The use of fluids may be tried, such as large amounts of coffee or water and the tension measured within one hour following the ingestion of these fluids.

(3) The use of mydriatics has been advocated but has been found to carry a definite risk as one may precipitate an acute attack of glaucoma necessitating immediate surgery.

Miotics when indicated should be used in the weakest strength possible to control the tension. One should start with a weak solution such as 1 per cent pilocarpine, and use it every three to four hours. The stronger miotics such as eserine should not be used in the early cases of glaucoma, and for prolonged cases pilocarpine is preferable to eserine because of the severe pulling sensation that the eserine causes. Some of the newer miotics such as 10 per cent furmethide and D.F.P. (0.1 per cent) may be tried.

Summary

Glaucoma always should be suspected and its presence or absence determined by examination. This is particularly important for the chronic simple type, which is too often overlooked. If a patient reports seeing halos around lights, if there is a history of frequent changes of glasses, or if there is a scratchy sensation in the eye for which no cause can be found, a careful study of visual fields and the measurement of the intraocular tension of the eye by means of a tonometer is essential.

Treatment of glaucoma may be either medical or surgical. All patients should have a complete physical examination and laboratory studies to eliminate any possible associated cause. Once the diagnosis of glaucoma has been established the patient should be informed of his condition and warned that it will require constant attention for the rest of his life. He should be encouraged to use his eyes normally but not to the point of fatigue. When diagnosis is made early and appropriate treatment started promptly most patients with glaucoma can retain reasonably satisfactory use of their eyes for many years.

References

1. Albaugh, C. H., and Dunphy, E. B.: Cyclodiathermy; operation for treatment of glaucoma. Arch. Ophth. 27:543-557 (March) 1942.
2. Barkan, O.: Operation for congenital glaucoma. Am. J. Ophth. 25:552-568 (May) 1942.

INTESTINAL INTUBATION*

T. GRIER MILLER, M.D.
Professor of Medicine, University of Pennsylvania

SINCE its development in 1934, intestinal intubation has been modified considerably and workers, both in our clinic and elsewhere, have accomplished by means of it many things not originally in mind.

Intestinal intubation did not originate with Dr. Abbott and me, although we made it a practical procedure by developing a double lumen tube and attaching to that an inflated balloon. The balloon made it possible for us to enter the small bowel quickly, instead of taking three or four days as had been necessary previously. It also served as a means of recording pressure changes in the tract, and at the same time the double lumen tube supplied an extra lumen through which we could make unrestricted extractions of the bowel contents.

The first person to do intestinal intubation, so far as I know, was a Netherlands physician by the name of Scheltema. In 1908 he realized the possibilities from his observation of a horse hair protruding from both ends of the alimentary tract of a chicken. He also had observed strings dangling from the anus of dogs and cats. These important observations led to the development of the technic of inserting a mercury-filled tube through the alimentary tract of the frog and taking x-ray films to show it. Dr. Scheltema then performed a like experiment in a child.

Within the following year or two Dr. Max Einhorn, of New York, developed what he called a "duodenal pump." His objective was to secure material from the duodenum for the study of the pancreatic secretions. Later, in 1919, Dr. Einhorn intubated the bowel beyond the duodenum, developing his jointed tube for that purpose. This tube was unnecessarily long because at the time he did not realize that a tube of 10 feet length was sufficient to intubate the entire digestive tract. He succeeded in reaching the cecal area.

In 1920 when Dr. Einhorn's jointed tube became available, I was able to intubate the small intestine in the same manner he had. The first difficulty encountered was that the tube had such a small lumen it was impossible to secure intestinal contents in such quantity as to make the procedure worthwhile. The second problem was that it took four to five days to accomplish the intubation and the patients by the end of that time were usually completely exhausted.

I did not resume the matter until 1930. At that time Dr. Abbott wished to study the effects of drugs on the duodenum. For this purpose he attached a rubber condom to the end of a tube, inserted it in the duodenum, distended the bag and made kymographic records as he gave the patients a variety of

**Lecture delivered October 9, 1948 at the Bunts course on Diseases of the Digestive Tract at the Cleveland Clinic (slightly abridged from wire recording).*

drugs. He finally became discouraged because the bag continued to slip from the duodenum down into the jejunum each time the apparatus was set up and things seemed to be progressing favorably.

Eventually I suggested that he allow the bag to slip and observe the result. By this method of simply releasing the bag a roentgenogram taken four or five hours later showed the balloon to be in the cecum.

Thus more or less accidentally we discovered how easy it is to intubate the small intestine. The next step was simply to tie another tube to the side of the first one, just behind the bag, and allow the patient to swallow it. This descended into the terminal ileum and completed the principle of a new technic.

To simplify the procedure we developed the double lumen tube although it took a year to obtain a satisfactory one. Up to that time the rubber manufacturers had never made a double lumen tube, except for the short one employed by urologists, and considered it an impossible thing to do. Finally, by an extrusion process (the shorter ones having been molded over glass rods), a manufacturer undertook the production of the double lumen tube now in routine use.

The procedure is as follows: one lumen is connected with the balloon, and through this lumen the balloon, once it has entered the duodenum, is inflated. The peristaltic waves of the duodenum then take charge and push the foreign body to its destined position. Once the tube is in the desired place, the other lumen, open at its distal end, is used for the extraction of material from the intestine or for the introduction of fluids. The bag and its attached portion of the tube may be used for recording peristaltic waves on a kymograph.

It is also possible, instead of using the second lumen for the extraction of material, to put another rubber bag around its terminal aperture and so secure kymographic tracings from two parts of the small bowel simultaneously.

In the study of the small intestine we found that at the duodenal level the contents had an average reaction of about pH 6, while, as lower levels were reached, it became neutral, always being practically neutral at the terminal ileum.

We also studied the osmotic pressure, taking samples from different places along the tract. As lower levels were reached the osmotic pressure became nearer and nearer to the normal osmotic pressure of tissue fluids, about 300 milliosmoles. The osmotic pressure of the bowel contents is largely due to its chloride and bicarbonate content.

Glucose entering the small intestine tends to push the osmotic pressure above the normal level. We found that, under such circumstances the chlorides drop although the bicarbonate does not change much. Thus the osmotic pressure in the intestinal contents is not radically altered. As soon as one electrolyte enters another is displaced, and so nature maintains a more or less fixed osmotic pressure.

Later Dr. Richard Warren, devised a technic for blocking the pylorus. However, experiments proved extremely difficult and he spent a year perfecting the technic. The stomach appeared to displace anything inserted from the pyloric end, either throwing it back into the body of that organ or shooting

it through into the duodenum. He finally succeeded only by putting down a tube with two bags attached, getting one bag just above the pylorus and the other bag just below, then blowing up both of them. An extra tube, running alongside and beyond the distal balloon enabled him to determine whether or not any fluid was getting past the pylorus. Even with this technic he failed often, but in some instances he was able to block the pylorus completely. Under such conditions he was able to introduce a glucose solution, determine how much of it was absorbed and how much fluid was poured out into the stomach to dilute it. Relatively little sugar was found to be absorbed in the stomach, and yet the concentration of the sugar in the stomach was reduced. This was due to a considerable increase in the volume of the fluid. When he put in only 200 cc. of a glucose solution he was soon able to extract 400 cc., the stomach obviously pouring out fluid to reduce the osmotic pressure of the solution.

An even more elaborate technic was finally worked out for isolating the duodenum. Trained people became expert in assisting and swallowed as many as three or four tubes at a time. This could hardly be accomplished with the ordinary patient. One tube was used to extract from the stomach any material that might get back to that organ. Another little tube was employed for the introduction of the glucose solution directly into the duodenum, and if any of that were regurgitated back into the stomach, it was picked up by the first tube. Still another tube was used to control a bag which blocked the jejunum just beyond the Treitz ligament area. A final larger tube permitted extraction of the duodenal material. By this technic we were in a position to introduce a glucose solution into the first portion of the duodenum and to collect from its distal portion such material as reached that level.

It became apparent that an enormous amount of sugar can be absorbed in the duodenum, and also that additional fluid is poured out from the wall of the duodenum further to dilute the sugar present. This obviously is a means that nature has developed to prevent a hypertonic solution from getting in the small bowel. Consequently, no matter how hypertonic a glucose solution may be on admission to the stomach, its tonicity is slightly reduced in that organ, further reduced in the duodenum, and by the time it gets to the jejunum it is isotonic with the tissue fluids.

By means of two tubes, one three-lumened and one two-lumened, we were able to collect material at the same time from different areas in the stomach, the duodenum and the upper jejunum and to determine the glucose content of each. The accumulated data on material from the stomach, duodenum and the upper jejunum indicate that no matter what the glucose concentration in the stomach (15 to 50 per cent) it is reduced to about 6 per cent as it reaches the jejunum. That is not in excess of 300 milliosmoles, which represents the normal osmotic pressure for the small intestine. Meanwhile in the duodenum the concentration was in the neighborhood of 13 per cent, which has been shown by other workers to be optimal for absorption from that organ. These are not new observations except that they have been made on the human subject.

In a discussion of some clinical applications of the work let us consider the "dumping syndrome," which so frequently follows a gastric reaction. Dr. Machella has worked out the mechanism of this disturbance. Usually the symptoms develop as soon as the patient starts to take food. He becomes nauseated, has a sense of fullness or discomfort, and sometimes pain, in the epigastrium. He often has a generalized feeling of warmth, and yet his forehead is cold and clammy. Diarrhea frequently follows. Because in some cases hyperglycemia has been discovered and in others a late hypoglycemia, it has been considered that the syndrome might be due to a disturbance in the sugar metabolism. What actually occurs is that hypertonic material goes directly from the stomach into the jejunum, where under normal conditions it is isotonic with the blood plasma. The duodenum which ordinarily reduces the concentration to a level that is acceptable to the jejunum, is out of the picture after a gastrectomy, and so this hypertonic material without the usual change drops directly from the stomach into the jejunum. There it sets up certain abnormal reactions and an enormous outpouring of fluid into the jejunum occurs in an attempt to bring the concentration down to the proper level. This sudden increase in volume has been demonstrated by injections into an isolated jejunum loop. The excessive quantity of fluid overdistends the jejunum and so causes distress and nausea. Secondly, nature tries as quickly as possible to absorb the excess sugar that is present, in order to reduce the osmotic pressure to a normal level. This accounts for the hyperglycemia. Moreover, nature attempts to disperse the hypertonic material throughout the tract in order to bring it into contact with a larger intestinal surface so that the sugar can be more readily absorbed. This results in diarrhea.

The management of the "dumping syndrome," is simply the withholding of food from the patient in a hypertonic state or delaying its admission to the jejunum. For the latter purpose reoperation has been resorted to in some instances, narrowing the aperture between the two organs.

A brief discussion seems indicated about our experience with patients having intestinal obstruction. Dr. Abbott and Dr. Charles G. Johnston first suggested that intubation might be performed in such patients. The difficulty, however, lies in the passage of a tube and a balloon down the small bowel when that organ is enormously distended. It is true that the distended intestine loses its peristaltic activity, but it must be remembered that wherever the tube goes, the contents of the bowel are siphoned off. With a properly arranged apparatus this aspiration occurs just distal to the balloon. Thus the balloon itself, being proximal to the open lumen, is always in a deflated part to the intestine, and as the bowel is deflated its peristalsis returns. This explains the onward progress of the tube in obstruction. It occurs only as the distention is relieved. With an atonic condition of the bowel wall in what is known as adynamic obstruction, the wall really is not paralyzed. It is simply so distended that it cannot function, and as soon as the contained gas or fluid is removed the bowel functions again and the peristalsis is in normal direction. The idea that antiperistalsis develops when the bowel is obstructed is erroneous. No

one has observed antiperistalsis in the small intestine below the middle of the duodenum.

We do observe fecal vomiting, however, which indicates that in some way the feces get back from the lower part of the intestine into the stomach. An English physician, Dr. Brinton, explained this as far back as 1880, before we knew about intubation. He illustrated the mechanism by a perforated piston in a syringe, the piston pushing downward but allowing the liquid contents of the syringe to come upward through the perforation. In intestinal obstruction the waves come down from above, but push the bowel contents against the blocking lesion which causes the contents to go backward as a central stream. Dr. Brinton, in further support of his theory, gave animals with an obstruction castor oil orally, and by puncturing the bowel just above the obstruction observed that the castor oil had descended that far before coming up again. Thus he demonstrated that the vomitus in such cases actually did come from the area of the obstruction, and peristalsis obviously carried it to that level.

In regard to intubation studies on drug effects, there has been a controversy among pharmacologists as to the result of morphine on the digestive tract. Some believe it causes contraction, while others insist that it brings about relaxation. Dr. Abbott investigated by intubation its action on the duodenum. With the balloon inflated in the duodenum and connected with a kymograph, he gave the patient ¼ gr. of morphine. The duodenum contracted and remained so for about fifteen minutes, but then began to relax and soon was more relaxed than before the drug was administered. This condition persisted for an hour or more. The same reaction, occurred lower in the tract. Thus obviously the drug is capable of producing both effects. It causes contraction, but the contraction occurs for only about ten or fifteen minutes and is followed by a period of an hour or more when the wall is relaxed. This suggests that it is unwise to administer morphine to a patient who has a bleeding duodenal ulcer, the bleeding being more readily controlled when the wall, gastric or duodenal, is tonic.

Later Dr. Kendall Elsom made similar studies on the effects of atropine on the duodenum, small intestine and colon. He was able to confirm in man its relaxing effect, previously demonstrated conclusively in animals. The effects of pitressin on the small and large intestine also were investigated by Dr. Elsom. In one patient the balloon reached the splenic flexure of the colon, and it was possible to secure roentgenograms that showed the balloon distended and, after administration of the drug, definitely contracted. Simultaneous records from the terminal ileum and the colon seemed to indicate that the contractions in the two parts of the tract, due to the pitressin, occurred alternately. Pain sometimes accompanied the contractions of the colon.

Dr. Elsom also devised an ingenious metal bucket for studies of intestinal digestion. This could be opened or closed by pressure changes in the lumen of the tube to which it was attached and could be introduced into the bowel. To measure the extent of the digestion of protein he inserted a calculated quantity of meat into the bucket, closed it and then passed it to a designated

part of the intestine. There the perforations in the bucket were opened to allow the entrance of bowel contents. After a fixed time the bucket was again closed and removed. By such a means he seemed able to demonstrate, in ulcerative colitis patients, some impairment of protein digestion in the small intestine, an important observation if confirmed.

A procedure has been developed by Dr. Machella involving intestinal intubation for the management of stubborn cases of chronic idiopathic ulcerative colitis. It allows the administration of a highly nutritious liquid diet and the removal, by an in-lying tube, of such residue as reaches the terminal ileum. Thus it affords a means of supplying the needed fluids, calories and nitrogenous materials, and at the same time permits rest to the diseased colon. Recently Dr. Machella has been giving the patients an amigen-dextrimaltose mixture and in most instances has obtained gratifying results.

INTRACRANIAL CYSTICERCOSIS

Report of a Case with Operation

WM. A. NOSIK, M.D. and R. J. GOODALL, M.D.
Department of Neurosurgery

THE possibility of infestation of the alimentary tract by the pork tapeworm (Taenia solium) is well recognized, particularly in those areas and countries where poor sanitation and lack of meat inspection exist. Less commonly recognized clinically is the fact that the larval form of Taenia solium, i. e., Cysticercus cellulosae, may also infest the nervous system and its coverings.

Africa and Cruz[1] quote Vosgien who reviewed 107 cases of Taenia solium infestation and found that the nervous system was involved in approximately 40 per cent. Dressel[2] observed that the brain was affected 72 times in 87 cases, or 82 per cent. Hennenberg,[3] in reviewing 1408 autopsies at the Charité in Berlin, reports only 3 cases of cysticerci of the brain having been found. Hare[4] of this country relates 2 cases in a large series of autopsies from the Presbyterian Hospital and the Neurological Institute of New York. Arana and Asenjo[5] of Chile found 25 cases of brain cysticercosis in a total of 202 intracranial tumors.

While the relative paucity of intracranial infestation in this country offers testimony to the sanitary systems in effect, such infestation is nevertheless possible.

MacArthur[6] referred to this condition as a possible cause of epilepsy and Forster[7] reported a case of insanity with epilepsy following infestation by Cysticercus cellulosae. Brailsford,[8] in 1925, showed that evidence of the parasite could often be obtained by radiography. He intimated that four or five years may elapse before the deposition of calcium in the cysts occurs, if indeed such deposition occurs at all.

The diagnosis of intracranial cysticercus may be difficult, largely because the infestation may be limited to one lesion or due to multiple lesions. Likewise, the infestation may involve the meninges, the cortex, or the white matter. The lesion may be found in the ventricular system as well and cause obstructive symptoms.

Kuchenmeister, as reported by Krause,[9] noted that in 88 cases of brain cysticercosis, the meninges were involved in 49, the cortex in 59, the ventricles in 18, and the white matter in 19 cases.

The symptomatology is extremely variable since it is dependent upon the location of the lesion or lesions. The number of the cysts and/or their location may vary to influence the clinical picture. While racemose clusters of the cysticerci are most common in the basilar cisternae, those in the supratentorial regions are usually intraparenchymal[5] and may give signs referable to these areas.

The state of the larva may also alter the clinical findings. MacArthur believes a patient may live for years with cysts within the cerebrum and experience little disturbance. However, when the parasite dies, symptoms may be caused by toxic effects or by an increase in the size of the cyst. The flaccid and unpalpable cyst absorbs fluid at that time and tends to become enlarged and tense.

When the cysticercus develops in the skin or muscle, the demonstration of the larval form of T. solium in the excised cyst may clarify the diagnosis quickly in a patient suspected of this condition. Since calcification of the cysts occurs more rapidly in the skin and muscle when these organs are involved, it may be possible to demonstrate the presence of this condition by the roentgenogram. Skin tests and complement fixation tests are generally regarded as unsatisfactory.

The difficulties encountered in arriving at this diagnosis in one patient are related here. Until the lesion was disclosed at operation, it was believed the findings were consistent with a diagnosis of meningo-encephalitis. The chronicity and the clinical course appeared to substantiate this impression.

Case Report

A 32 year old woman, born in Italy, had emigrated to the United States at 11 years of age. She lived in a nearby large city and had not left the country at any time. She was first seen at the Cleveland Clinic on August 19, 1944 complaining of pain on the left side of the face and neck and in the suboccipital region, of three months' duration. The strain of a difficult domestic situation caused her to be extremely nervous. There was a complete lack of objective findings. A functional basis for her complaints was entertained at that time by one examiner.

She was again seen on June 22, 1946 complaining of headaches, pain in the left face and left ear and in the occipital region. There was an associated stiffness of the neck. She had developed a lateral diplopia in the previous three weeks. There had been some nausea but no vomiting. A general physical examination disclosed no abnormalities. Pertinent findings in the neurological examination showed bilateral papilledema of 2 to 3 diopters. The ophthalmologist was of the opinion that the fundus had the appearance of a severe neuroretinitis. There was a hyperreflexia of the left lower extremity only. The Babinski test was positive on the left while the Romberg test was negative. X-ray of the skull showed no abnormality. It was believed that, while a meningo-encephalitis must be considered, the lesion was more likely an intracranial neoplasm affecting the right parietal area. To differentiate between an inflammatory or neoplastic lesion, a pneumo-encephalogram was done on June 14, 1946. The ventricular system was well outlined and was normal in shape and position with no displacement. The third and fourth ventricles as well as the aqueduct were normal. The basilar cisternae were normal. There was no evidence of a space-filling lesion. Examination of the fluid showed 300 white cells of which 60 per cent were lymphocytes, with no globulin, and a total protein of 41 mg. per cent. It appeared that the patient had an inflammatory lesion in the nature of a meningo-encephalitis. She was given three x-ray treatments during which she experienced discomfort in her left arm. The appearance of the optic disks improved considerably. Before she was discharged from the hospital, another lumbar puncture was made on June 22, 1946. Although she seemed clinically improved, there were 280 white blood cells in her spinal fluid. The protein was 45 mg. per cent. Special cultures were made on the fluid which were all negative for bacteria or fungi.

She was readmitted to the hospital on July 15, 1946 stating that the frequency of pain on the left side of her head was less but the intensity was greater. Lumbar puncture showed increased pressure with a high Ayala index. On July 18, 1946, a left subtemporal decom-

pression was done, and following this operation, the patient was relatively free of headache. A pneumo-encephalogram was again made on July 24, 1946, and showed no evidence of an intracranial lesion. Postoperative visual fields indicated some enlargement of the blind spots bilaterally. There was no change in the neurological examination. The spinal fluid contained 30 lymphocytes. Following some x-ray treatment, the patient was completely free of pain. At the time of discharge on August 5, 1946, the spinal fluid pressure was normal.

Subsequently, she was readmitted to the hospital for several short periods during which lumbar punctures were done. The pressure remained in the vicinity of 190 mm. of water and contained from 65 to 150 white blood cells. She was given a series of six typhoid shocks and had a good reaction to this treatment. She was dismissed from the hospital on October 6, 1946, apparently improved.

She was seen as an out-patient on December 4, 1946. Her headache was gone. She was troubled only by a slight intermittent pain behind the left ear. Neurological examination was entirely within normal limits.

On August 8, 1948, she was again admitted to the hospital because of postauricular pain on the left as well as a swishing noise in her left ear. Neurological examination revealed the presence of a low-grade papilledema, and a moderate degree of tension in the left subtemporal decompression. Lumbar puncture revealed an initial pressure of 220 mm. of water. Twenty-four lymphocytes were present in this fluid and 33 mg. of protein. The smear and culture were negative for organisms. The stained sediment showed no tumor cells. The spinal fluid sugar was 49 mg. per cent with 693 mg. per cent chloride. A pneumo-encephalogram again was made which showed a diffuse dilatation of the ventricular system with no evidence of an obstructing lesion. Because of the papilledema and increased pressure, a right subtemporal decompression was performed on August 12, 1948. Histoplasmin and coccidiodin

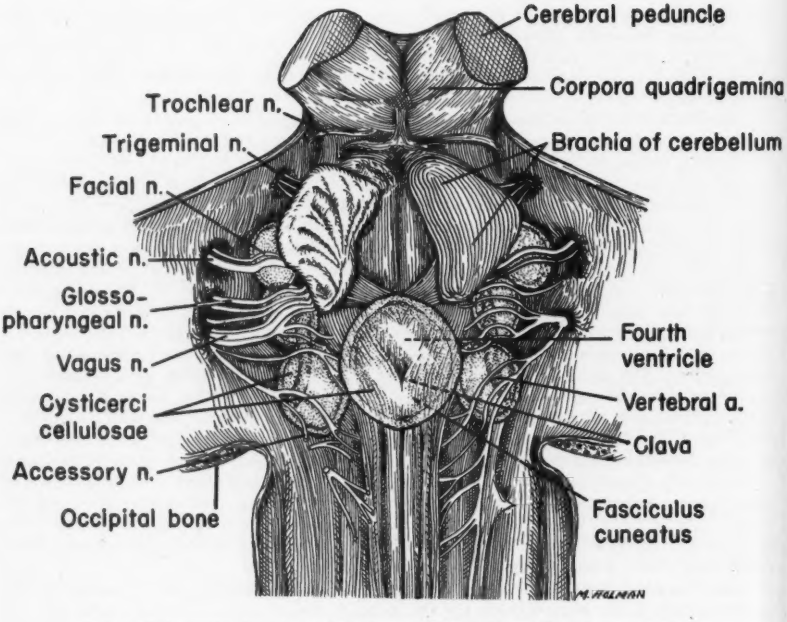


FIG. 1. Schematic drawing indicating position of cysts found at operation.

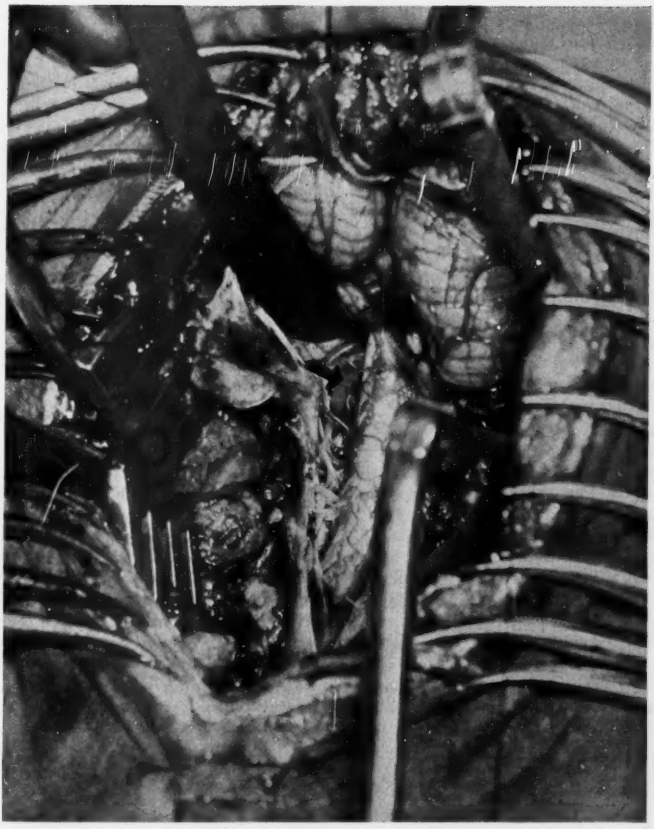


FIG. 2. Operative exposure on left showing one cyst (indicated by arrow) beneath the vagal root filaments.

skin tests were negative. The patient made a satisfactory recovery and was discharged on August 21, 1948. The diagnosis was still considered to be chronic meningo-encephalitis.

She was symptom-free until October, 1948, when, while vacationing, she developed a severe headache. There was nausea but no vomiting. The subtemporal decompression areas were extremely tense. She was observed in another hospital where a diagnosis of increased intracranial pressure, cause unknown, was made, and lumbar puncture performed to relieve the pressure.

She was returned again to the Cleveland Clinic Hospital on October 18, 1948. The only pertinent physical finding was the presence of a mild degree of papilledema and a bulging of the decompressions. Lumbar puncture was repeated which showed an initial pressure of 360 mm. of water. A pneumo-encephalogram was again made on October 22, 1948 which indicated the presence of a nonobstructive internal hydrocephalus of considerable degree and a lack of cortical filling. The lateral ventricles as well as the third and fourth ventricles

were well visualized. In the course of the pneumo-encephalogram proceedings, the flow of cerebrospinal fluid appeared to come in spurts of approximately 20 cc. volume as if an intermittent obstruction was present. The dilatation of the ventricles had increased considerably over the encephalogram of August 12, 1948. A suboccipital exploration was elected on October 27, 1948. Upon opening the arachnoid, a large round opalescent cyst was dislodged from the midline in the area of the fourth ventricle. This fluid-containing cyst was approximately 3.0 cm. in diameter, and lay free in the subarachnoid space. It was at that time that the clinical diagnosis of an intracranial parasitic infestation was made. This diagnosis was confirmed by subsequent microscopic study. Numerous other cysts were noted in the posterior fossa as depicted in the drawing (figs. 1 and 2). The pathologic report indicated later these were cysticercus cellulosae. A total of seven such cysts were removed at this operation with no further lesion being observed. Exploration of the fourth ventricle revealed a free flow of fluid mixed with air emerging from the aqueduct area. The patient had a relatively uneventful convalescence and was discharged from the hospital on November 7, 1948. Spinal fluid pressure at the time of discharge was 170 mm. of water.

She was examined again on December 13, 1948 and was free of pain. However, she was troubled with vomiting which occurred shortly after eating. The decompressions were soft and the optic disks flat and pallid. The deep reflexes were slightly hyperactive. She was given symptomatic treatment.

When seen again three weeks later, the patient stated that the decompressions had begun to bulge again in both temporal and suboccipital areas. There were short periods of disorientation and some staggering in walking. Attacks suggestive of right Jacksonian type were present. The optic disks showed some slight degree of elevation. The spinal fluid pressure at this time was 270 mm. of water. Her symptomatology increased and she was again admitted to the Cleveland Clinic Hospital on January 17, 1949, the pertinent findings consisting of bulging of the decompression sites, hyperactive deep reflexes, equivocal bilateral Babinskis, and a lateral nystagmus. A lumbar puncture was done again which showed a pressure range from 270 to 400 mm. of water. On January 24, 1949, a pneumo-encephalogram was made which showed a complete block in the posterior fossa. The suboccipital decompression was then reopened and a remarkable degree of scarring was present throughout the posterior fossa. The entire cervical cord, the medulla and the base of the cerebellum were enveloped in a funnel-shaped, fibrinous appearing membrane approximately 1 to 2 mm. thick. This membrane was dissected free until fluid was observed to flow freely from the fourth ventricle region. Further inspection revealed no evidence of cysts. The Torkildsen procedure was elected, the tube being brought subosteally from the posterior portion of the right lateral ventricle into the cisterna magna area. Dye studies before closure indicated the patency of the tube.

The first day postoperatively, the course was satisfactory. The second day postoperatively, the decompression areas were noted to be bulging and lumbar puncture was done. The normal appearing spinal fluid of the day before was replaced with a thick, syrupy, yellowish fluid. Supportive treatment was instituted. On the third postoperative day, a similar finding was made both in the lumbar region and in the ventricular region. The patient lapsed into unconsciousness, grew progressively worse and died on January 28, 1949.

The postmortem examination was limited to a reopening of the incision which disclosed a necrosis of pronounced degree in the inferior cerebellar area. A considerable amount of liquefaction was also found. In the exploration of the posterior fossa, a group of cysts was recovered from the prepontine cistern area. Incisions were made from below into the posterior portion of the ventricles and a limited examination failed to uncover the presence of any cysts in the ventricles although obviously, the examination was inadequate.

Comment

In this patient repeated examinations failed to show any evidence of Taenia solium infestation even after the diagnosis had been established. X-ray studies of the soft tissue showed no calcifications. Stool studies disclosed no

abnormalities. From the history, the variable clinical picture, the laboratory findings, the cellular response in the spinal fluid as well as response to fever and x-ray therapy, it was believed that this patient had a meningo-encephalitis of undetermined type until the diagnosis was clarified at operation.

Arana and Asenjo[5] believed that the presence of an internal hydrocephalus, absence or displacement of the ventricular system, especially of the aqueduct, partial obliteration of the aqueduct and fourth ventricle with the presence of air in both and in the cisterna magna, associated with clinical, biological and laboratory examination were diagnostic of cysticercosis of the brain. The various air studies made in this patient were carefully reviewed and evaluated, but no changes suggestive of those described by these writers were found.

Generally, surgical experiences in this condition have not been encouraging. Arana and Asenjo[5] as well as Ray[11] and Ritchie[11] of this country have reported cases benefited by surgery.

Dandy[12] and Cairns[13] each report 2 cases in which operation was unsuccessful. To this group we must add our own unsuccessful experience.

When an isolated cyst is the cause of a focal disturbance, surgical intervention may be of some benefit. When the obstruction to the cerebrospinal circulation is due to the presence of intraventricular or multiple cysts in the posterior fossa, it is believed that surgical removal of as many cysts as possible in conjunction with the use of the Torkildsen procedure may be of value in an otherwise discouraging situation. Further experience is necessary before the effectiveness of this suggestion can be evaluated. It might well serve as a temporizing measure, if one recalls MacArthur's observation that a later resorption of fluid from the cyst occurs. Whether resorption of fluid takes place in the same manner when the cysts are located in the cerebral parenchyma or subarachnoid space as it does when the skin or muscle are involved, remains to be demonstrated.

The clinical course here was suggestive of an inflammatory reaction, i. e., possibly toxic, which led to the diagnosis of meningo-encephalitis. The death of the larva may well have been responsible for the findings. The development and progression of obstructive symptoms and signs may be inferred to have been due to the enlargement of the cysts by fluid absorption. Whether or not a reabsorption of the fluid from the cysts would have occurred later cannot be ascertained.

Conclusion

1. A patient with cysticercosis of the posterior fossa was unsuccessfully treated surgically.

2. The use of the Torkildsen procedure in conjunction with a thorough evacuation of the cysts is suggested for this type of case when multiple cysts are present in the posterior fossa.

3. When the obstructing lesion is intraventricular in position and craniad the fourth ventricle, the Torkildsen procedure alone may suffice.

References

1. Africa, F. M., and Cruz, J.Z.S.: Cysticercus cellulosae in man. J. Philippine Islands M.A. 7:209-215 (June) 1927.
2. Dressel, J.: Zur Statistick des Cysticerkus Cellulosae (Berlin: G. Schade, 1877).
3. V. Hennenberg, R.: Die tierischen Parisiten des Zentralnervensystems. Bumke u. Foersters, Handb. Neurol. 14:286-352, 1936.
4. Hare, C. C.: Cysticercus cellulosae of brain. J.A.M.A. 111:510-515 (Aug. 6) 1938.
5. Arana, I. R., and Asenjo, A.: Ventriculographic diagnosis of cysticercosis of posterior fossa. J. Neurosurg. 2:181-190 (May) 1945.
6. MacArthur, W. P.: Cysticercosis as seen in British army with special reference to production of epilepsy. Roy. Soc. Trop. Med. and Hyg. 27:343-363 (Jan.) 1934.
7. Forster, E. B.: Insanity with epilepsy following infestation by cysticercus cellulosae. Brit. M.J. 2:543 (Oct. 12) 1946.
8. Brailsford, J. F.: Cysticercus cellulosae—its radiographic detection in musculature and central nervous system. Brit. J. Radiol. 14:79-93 (March) 1941.
9. Krause, F.: Die allgemeine Chirurgie der Gehirnkrankheiten (Stuttgart: F. Enke, 1914) p. 34.
10. Ray, B. S.: Cysticercosis of brain. Arch. Neurol. and Psychiat. 45:494-504 (March) 1941.
11. Ritchie, W. P., French, L. A., and Titrud, L. A.: Cysticercosis; case report. J. Neurosurg. 2:543-546 (Nov.) 1945.
12. Dandy, W. E.: Cysticercus cellulosae. In Lewis, D.: Practice of Surgery (Hagerstown: W. F. Prior Company), 12:399-404, 1932.
13. Cairns, H., cited by MacArthur.[6]

THROMBOPENIC PURPURA

Parathyroid Hormone in the Treatment of a Case

JOHN D. BATTLE, JR., M.D.
Department of Medicine

IN 1932 Lowenburg and Ginsburg[1] first reported an apparent beneficial result following the accidental administration of parathyroid hormone to a young patient with essential thrombocytopenic purpura. The dosage was sufficient to cause severe hypercalcemia and clinical signs of toxic overdosage. Again in 1936 these authors[2] obtained a similar clinical response following the subcutaneous administration of 60 units of parathyroid hormone daily for four consecutive days. Both patients had failed to respond to other measures such as transfusions and antivenin injections. In neither patient had splenectomy been performed prior to the administration of parathyroid extract.

Parathyroid hormone has been used at the Cleveland Clinic since 1940 as one of the methods of treatment in patients with thrombopenic purpura. This report concerns the first patient treated at the Clinic by the induction of hypercalcemia with parathyroid hormone. The patient reported here had failed to respond to all the usual methods of therapy including splenectomy.

Case Report

A 26-year-old housewife was admitted to the Cleveland Clinic Hospital on July 14, 1940, with complaints of excessive menstrual bleeding, profuse epistaxis, and bruising easily with slight injury. In February, 1940 she first noticed "black and blue" spots under the skin and several weeks later menorrhagia persisting for ten to fourteen days. In May, 1940 she developed prolonged and recurrent nasal and gingival bleeding which remained uncontrolled despite local measures of treatment.

The past history and family history contributed nothing pertinent. The menstrual cycles were normal prior to her present illness and she had never been pregnant. The patient had been hospitalized at home with a tentative diagnosis of idiopathic thrombopenic purpura and had failed to respond to liver extract, oral iron, intravenous calcium, snake venom (moccasin), or multiple transfusions. On detailed inquiry, she denied the ingestion of any drugs known to cause purpura preceding her illness.

Physical examination revealed an acutely ill young woman with moderate pallor and diffuse purpuric lesions of the skin and oral mucosa. Crusts of dried blood were evident in the nares and gingival bleeding was pronounced. The gums showed no hypertrophy. The thyroid was not enlarged nor was there generalized lymphadenopathy. Examination of the chest revealed the lung fields to be clear. The heart was not enlarged and the heart rate was 110 beats per minute with an audible soft apical systolic murmur. The abdominal examination revealed no abnormalities, the liver and spleen were not palpable. The remainder of the physical examination, including the pelvis and rectum did not reveal any abnormalities.

On admission her oral temperature was 101 degrees, pulse 110, blood pressure 118/70. The patient remained febrile, with the temperature fluctuating daily from 101 to 102 F. for the first sixty-five hospital days.

The red blood cell count was 1,450,000; hemoglobin 4.8 Gm. (Haden-Hauser), or 31 per cent of normal; white blood cells 6150 with 73 per cent neutrophilic leukocytes, 16 per cent

lymphocytes, 4 per cent eosinophils, and 7 per cent monocytes. The reticulocyte count was 31 per cent. The blood smear showed severe anisocytosis and poikilocytosis. No immature white blood cells were seen. The platelet count was 10,000 per cu. mm. by the Rees-Ecker method. Bleeding time was longer than one hour with no clot retraction in twenty hours. The coagulation time was twelve minutes by the Lee-White technic. Study of bone marrow smears obtained by sternal puncture revealed definite stimulation of erythropoesis, normal distribution of the myeloid cells, and an increase of megakaryocytes. The urinalysis was normal and the blood Wassermann and Kahn reactions were negative.

The patient was given several blood transfusions and splenectomy was performed by Dr. Robert Dinsmore on July 16. The immediate postoperative course was stormy with development of an atelectasis of the right lower lobe, persistence of low-grade fever, and failure of an increase of blood platelets. The platelet count remained between 10,000 and 20,000 for thirty consecutive postoperative days in spite of transfusions, calcium gluconate intravenously, and large doses of vitamin C. The epistaxis, gingival bleeding, and oozing about the incision continued. Two courses of "Koagamin" were given without benefit.

On August 14, the thirtieth postoperative day, parathormone administration was begun. At this time the base-line studies revealed the platelet count to be 10,000, blood calcium 9.2 mg. per 100 cc., and blood phosphorus 3.4 mg. per 100 cc. The patient received 150 units of parathyroid hormone (Lilly) intramuscularly the same day; 450 units on August 15, and 350 units on August 16 in divided doses every six to eight hours (figs. 1 and 2). On the date of the last administration, the gingival, nasal, and vaginal bleeding ceased, the platelet count rose abruptly to 120,000, and the blood calcium reached a peak of 13.9 mg. per 100 cc. During the three days of parathormone therapy, the patient was given daily intravenous injections of 10 cc. of 10 per cent calcium gluconate.

With the cessation of bleeding, the clinical course steadily improved despite the development of an intra-abdominal abscess which necessitated incision and drainage on September 30. Re-check study of the bone marrow by sternal puncture on August 29 revealed a diminution in the number of megakaryocytes with moderate hyperplasia of the erythroid and myeloid cells. The megakaryocytes appeared larger and more mature.

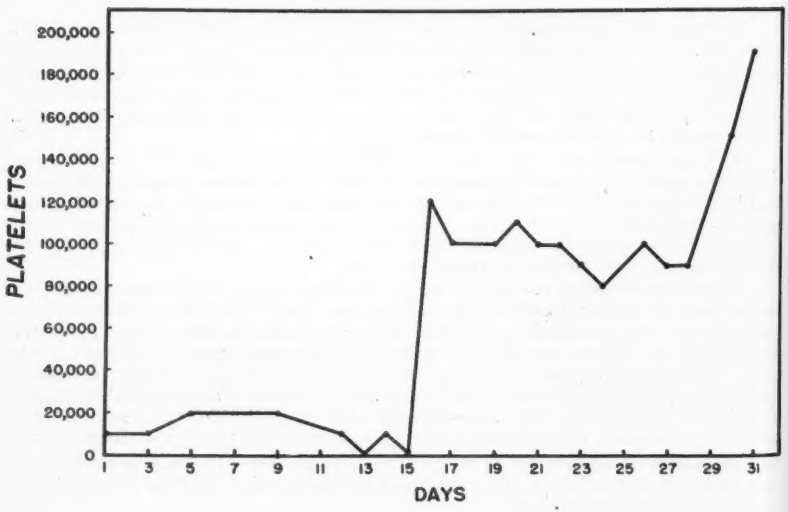


FIG. 1

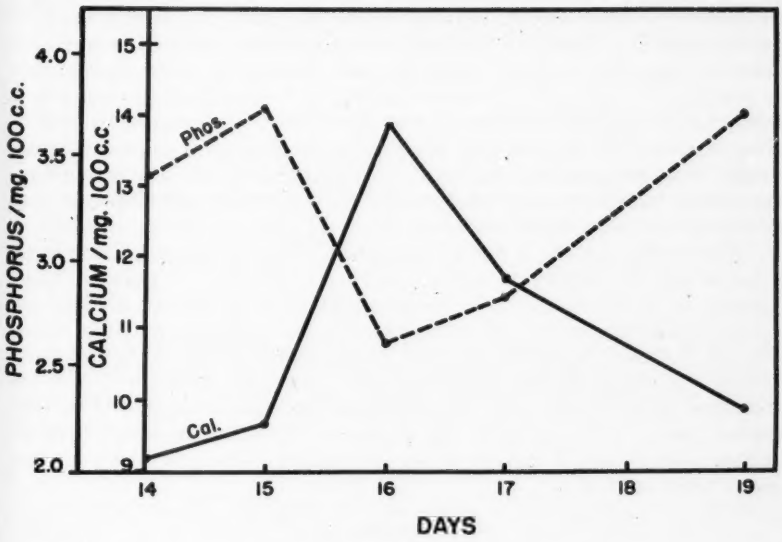


FIG. 2

The patient was discharged on September 28, 1940 at which time the blood studies were normal except for a moderate hypochromic anemia. The patient was last seen in August, 1948 and she stated that she had been entirely well since discharge and had had normal menstrual periods. No abnormalities could be found on physical examination, and the tourniquet test was normal. The complete blood count with hemorrhagic studies was also normal and the platelet count was 330,000 per cu. mm.

Discussion

The mechanism of the bleeding tendency in thrombopenic purpura is obscure. The number of circulating platelets is an important diagnostic feature in such patients, but the cause of the diminution in their numbers remains debatable. As the bone marrow studies usually reveal a normal or increased number of megakaryocytes, it has been suggested that the platelet deficiency is due to a maturation arrest of the megakaryocytes. Others believe that the circulating platelets are reduced because of excessive phagocytic activity of the spleen in this type of purpura. The exact role of capillary fragility with adherence of platelets to injured or diseased endothelium of the capillaries is not clear. It appears, however, to be a definite factor in many such patients.

With the production of hypercalcemia by parathyroid hormone, there has been an apparently dramatic increase of circulating platelets, decrease in bleeding time, and clinical improvement in a number of patients. This response appears to be due to the hypercalcemia, the latter representing an increase in the ionized fraction of the blood calcium. No quantitative relationship between

the level of the blood calcium and the number of circulating platelets has been demonstrated. In those patients in whom the administration of parathormone failed to cause a demonstrable hypercalcemia, the results have been equivocal or poor. Mathewson and Cameron[3] reported the occurrence of apparent parathormone inactivity in a patient given 300 units subcutaneously in divided doses at four day intervals with no increase in the blood calcium. Similar results in several patients to whom much larger quantities of the hormone were given have been observed here, but no satisfactory explanation of such apparent inactivity can be offered.

With few exceptions, including the patient reported, this method of treatment in essential thrombocytopenic purpura has been used prior to splenectomy. In those patients who failed to obtain a satisfactory clinical and hematological response to induced hypercalcemia, splenectomy was generally advised. Following splenectomy, these patients rarely failed to obtain a satisfactory response. Rosenthal[4] reported in 1937 the use of parathormone in the treatment of 7 patients with essential thrombocytopenic purpura. Five were chronic cases and 2 were acute. He stated that no beneficial results were obtained. The details of dosage of parathyroid hormone and blood calcium levels were omitted.

Technic

Prior to the administration of parathyroid hormone, the diagnosis of idiopathic thrombopenic purpura must be established beyond any reasonable doubt, and it is advisable that the patient be hospitalized. Following withdrawal of blood for platelet, calcium, and phosphorus examinations, the patient is given 100 to 200 units (1 to 2 cc.) of parathyroid hormone* intramuscularly. The blood calcium and phosphorus level is checked daily along with the platelet count. Subsequent doses are adjusted, depending on the clinical evidence of toxic effects of hypercalcemia, and on the blood calcium level. In children 100 to 200 units daily usually produce a significant hypercalcemia in 48 hours. In adults it is frequently necessary to give 200 units every six hours for three or four consecutive days, discounting the drug when a blood calcium level of 15 mg. per 100 cc. is reached. In the first group of patients treated, 10 cc. of 10 per cent calcium gluconate was given intravenously once or twice daily, to counteract, if possible, the rapid withdrawal of calcium from the bones. Additional calcium, either orally or parenterally, has not been used routinely in subsequent cases.

The toxic effects of acute hypercalcemia primarily consist of nausea, vomiting, and diffuse abdominal crampy pain, and they generally do not occur unless the blood calcium is above 15 mg. per 100 cc. The physiologic action of parathormone is not greater than twenty-four hours, and toxic effects subside rapidly upon cessation of the drug.

To date there is general agreement that the two procedures most likely to produce beneficial results are repeated blood transfusions and splenectomy.

*Lilly's.

There is little doubt that transfusions afford only temporary improvement. The results of splenectomy have stood the test of time, but it is recognized that all failures are not due to the presence of accessory spleens overlooked at the surgical procedure.

The clinical course of this disease is so variable, with relapses, unpredictable recovery, and inconstant severity, that the evaluation of any single form of treatment is difficult. It can be stated, however, that inducing acute hypercalcemia with parathyroid extract has apparently produced a satisfactory response in several patients with thrombopenic purpura and is worthy of further investigation.

Summary

A patient apparently recovered from thrombopenic purpura as a result of the induction of acute hypercalcemia with parathyroid hormone. Splenectomy performed thirty days prior to this treatment had been of no demonstrable value.

References

1. Lowenburg, H., and Ginsburg, T. M.: Acute hypercalcemia; report of a case. J.A.M.A., **99**:1166 (Oct. 1) 1932.

2. Lowenburg, H., and Ginsburg, T. M.: Induced hypercalcemia; its possible therapeutic relations to thrombocytopenic purpura. J.A.M.A., **106**:1770-1781 (May 23) 1936.

3. Mathewson, F. A. L., and Cameron, A. T.: An apparent instance of parathormone inactivity. Canad. M. A. J., **36**:141-148 (Feb.) 1937.

4. Rosenthal, N.: Course and treatment of thrombocytopenic purpura. J.A.M.A. **112**:101-106 (Jan. 14) 1939.

SKIN IMPRINTS IN CUTANEOUS LYMPHOBLASTOMA

JOHN R. HASERICK, M.D.
Department of Dermatology

BECAUSE of their accuracy, speed and simplicity in the diagnosis of cutaneous lymphoblastoma, tissue imprints deserve greater clinical application. Recently, 2 cases of lymphoblastoma of the lymphocytic type involving the skin alone have been diagnosed in the Department of Dermatology, and in each instance the tissue imprint provided specific and more rapid information than the routine pathologic preparation of the tissue from which the imprints were made. One of these cases is reported.

Case Report

A registered nurse, aged 59, was first seen in the Cleveland Clinic on December 29, 1948. She had been in good health until October 1, 1948, when she noted the onset of lumps in the skin of the right lateral thigh. Microscopic examination of one of these lumps was reported

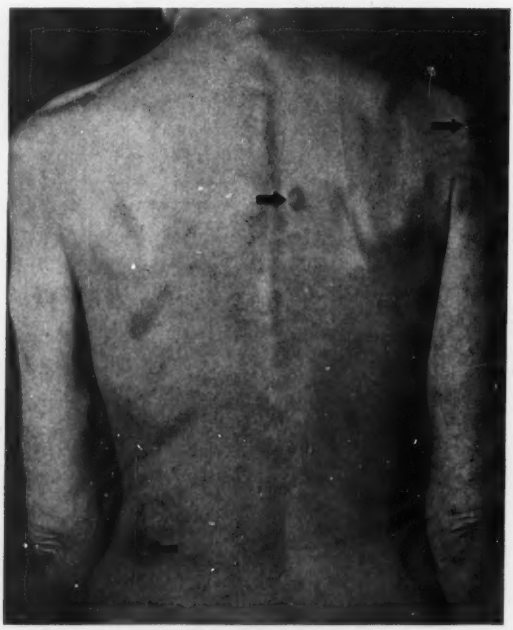


FIG. 1. Clinical appearance of lesions.

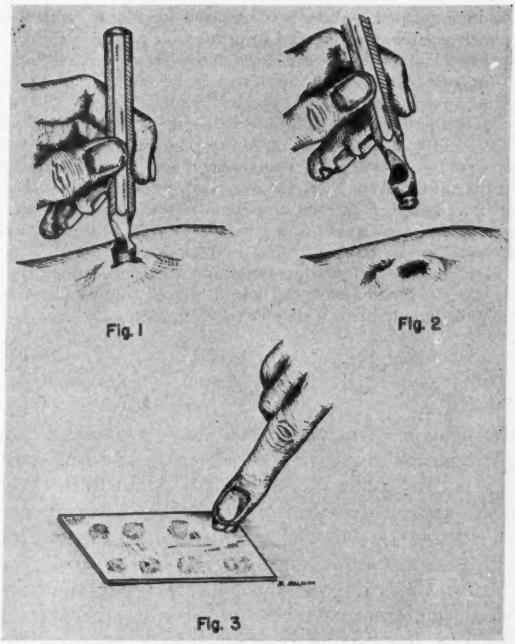


FIG. 2. Imprint technic.

as panniculitis. Other indurations appeared gradually at other sites, eventually involving most of the body and face (fig. 1). The lumps were indurated and bluish to purple in color. There was occasional pruritus. In December 1948 she developed many red streaks and patches of erythema which were attributed to phenobarbital. Stopping the drug had no effect on the lesions. A moderate degree of ankle edema developed. Her past history was non-contributory.

Physical examination revealed a well developed, well nourished tall white woman, weighing 120 pounds. Her temperature was 98.7 F. and the pulse rate was 100. The blood pressure was 120/68. The following positive findings were present: Moderately enlarged lymph nodes noted in the axillary, inguinal and cervical regions, thyroid diffusely enlarged, a soft grade II systolic murmur heard to the left of the sternum in the third and fourth interspaces. Dermatologic examination revealed diffuse blotches of erythema associated with bluish purple subcutaneous nodules. Periorbital edema was present as well as 2 plus ankle and sacral edema. There was no cutaneous atrophy. Laboratory studies were as follows: a specific gravity of 1.024 revealed by urinalysis; pH 5.5; absence of albumin and sugar; examination of the sediment revealed no cellular elements; the hemoglobin 11.5 Gm. per one hundred cubic centimeters and the erythrocyte count 4,360,000, with slight anisocytosis. The leukocyte count was 16,900 and the differential count showed 45 per cent neutrophils, 50 per cent eosinophils, 1 per cent lymphocytes and 5 per cent monocytes. The platelets were 340,000 per cu. mm. Bleeding and clotting time, prothrombin time and clot retraction studies were normal. Bone marrow examination revealed "Eosinophilia—all stages of development. No evidence of lymphatic leukemia." Roentgenologic examination of the chest was negative.

One of the most indurated nodules was removed for biopsy, with a round cutaneous punch. This specimen was blotted dry and imprinted on a clean defatted glass slide. The biopsy was reported by Dr. John B. Hazard, head of the Department of Pathology, as follows: "Cutis and subcutaneous tissue densely infiltrated by round cells which for the most part were of the size and appearance of small lymphocytes. Larger cells with a fairly abundant pink staining cytoplasm and a small well differentiated nucleus were present, and in addition to these, other cells with somewhat more cytoplasm than the small lymphocytes and with a vesicular, round to slightly indented nucleus were noted. Occasional to frequent mitoses were present. The cells of infiltrate were densely massed in the subcutaneous and deep corium, and were found in greatest abundance about vessels and secondary structures of the skin. A few polys, plasma cells and eosinophils were present in scattered locations. Pathologic diagnosis: Lymphoblastoma of skin, lymphocytic type." Examination of the imprint revealed large numbers of immature lymphoblasts, associated with many lymphocytes. The lymphoblast was the predominant cell and in general outnumbered the more mature forms. The nuclei of the lymphoblasts were pale staining, with fine clumping of the chromatin.

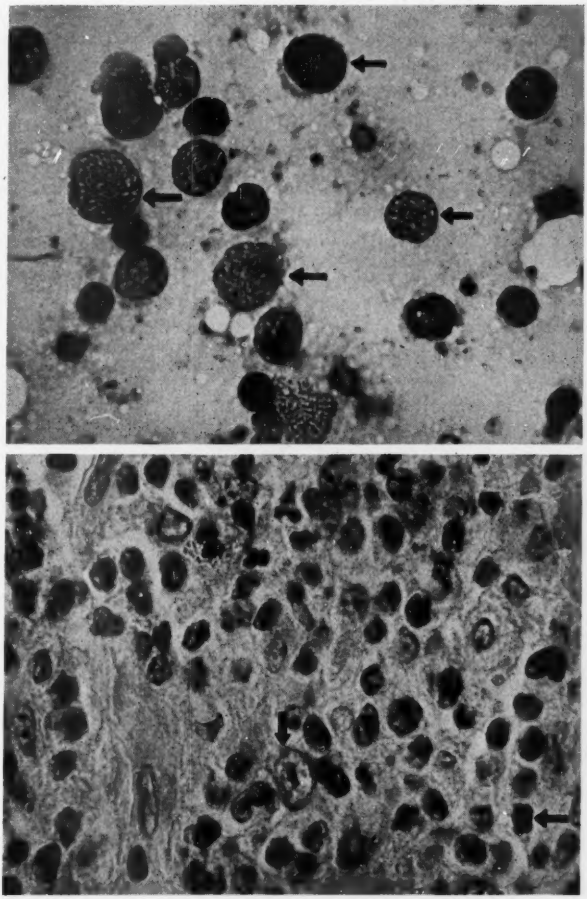
Comment

Prior to the tissue imprint in the previously mentioned case clinical difficulties were encountered in the diagnosis. Because of a biopsy report the referring diagnosis was "Relapsing febrile nodular panniculitis (Weber-Christian's Disease)." In this respect the case simulated closely one reported in 1942 by Reimann, Havens and Herbut[1] in which the diagnosis of Hodgkin's disease was established at autopsy but in which Weber-Christian's disease was considered during life. Cases of leukemia cutis in whom the bone marrow and peripheral blood are normal have been noted in the literature, and it is now a well established fact that lymphoblastoma of all types may first involve the skin alone. In such cases imprint and tissue studies are of utmost value. It should be emphasized, however, that such investigations are of positive assistance only when the cutaneous manifestations of the lymphoblastoma are specific. Nonspecific alterations such as excoriations, urticaria, pigmentations, bullous eruptions and exfoliative dermatitis usually contain nonspecific histologic findings and produce negative imprints. With specific involvement of the skin by lymphoblastoma the tissue imprint may definitely establish the diagnosis, though it may or may not provide the exact type as specifically as the usual pathologic sections. The imprint provides the most precise information in the lymphocytic type of lymphoblastoma. In Hodgkin's disease and mycosis fungoides the skin imprint may fail to provide as reliable information as the histologic section.

Technic

The tissue is removed with a dermatologic punch, precautions having been taken to select a typical indurated lesion. The fresh unfixed tissue is blotted to remove excess blood and then pressed firmly on a clean glass slide (fig. 2). This is repeated several times. The slides must be fixed rapidly by drying or gentle heat to prevent disintegration of the nuclear patterns. The slides are stained with Wright's stain in the usual manner (fig. 3 a and b).

(a)



(b)

FIG. 3. (a) Photomicrograph showing large immature stem cells (arrows); (b) Photomicrograph showing same cells in section (arrows).

Imprints from normal skin usually provide only torn collagenous bundles and a few cells of the fixed tissue variety. In imprints of leukemia cutis, or lymphosarcoma cutis, there is ordinarily an abundance of cells available for study. The entire procedure takes only a few minutes and it can be done easily in the office.

Summary

Specific cutaneous manifestations of lymphoblastoma may be diagnosed rapidly and accurately by imprinting the fresh unfixed tissue removed for biopsy. A case is reported in which these studies provided quick and valuable information. The technic is simple, inexpensive and merits wider clinical application.

References

1. Reimann, H. A., Havens, W. P., and Herbut, P. A.: Hodgkin's disease with specific lesions appearing first in skin. Arch. Int. Med. **70**:434-443 (Sept.) 1942.
2. Sweitzer, S. E., and Winer, L. H.: Ulcerative Hodgkin's disease and lymph node imprints. Arch. Derm. and Syph. **51**:229-236 (April) 1945.

PREFRONTAL LOBOTOMY FOR THE RELIEF OF INTRACTABLE PAIN; VALUE AND LIMITATIONS

Report of Five Cases

GUY H. WILLIAMS, JR., M.D.
Department of Neuropsychiatry

THE relief of pain has been one of the chief concerns of physicians since time immemorial. Medical history reveals the use of a wide variety of mechanical procedures, administration of substances such as herbs and drugs, as well as the employment of incantations and witchcraft to relieve discomfort. Fortunately, through the "growth process" of medicine, scientifically sound medications and surgical procedures have been developed to achieve the relief of pain. In the majority of painful conditions mitigation is achieved by the present day routine surgical and medical armamentarium. However, in certain cases of advanced diseases, as well as in some of the more severe disorders of the nervous and emotional systems, the usual measures of pain alleviation are inadequate.

Surgical methods, both conservative and radical, have been employed for the relief of pain with varying degrees of success. Within the past several years psychosurgery, originated in the modern sense by Moniz and Lima[1] in 1935 and pioneered in America by Freeman and Watts,[2] have afforded the neurosurgeon a new and more potent weapon to be used in cases where intractable pain, extreme anxiety and depression and accompanying drug dependence have become issues of paramount importance.

Numerous articles on prefrontal lobotomy have appeared in the medical literature. This discussion will not attempt to evaluate the procedure. The following case reports merely demonstrate that prefrontal lobotomy serves a useful purpose in the present day therapy.

Case Reports

Case 1. Intractable Pain from Carcinoma of the Mastoid

A 58-year-old white woman came to the Cleveland Clinic with a discharging right ear which had troubled her for four months. Originally she was treated for a chronic otitis media and otitis externa. However, inasmuch as the condition failed to improve within three to four weeks' time on the usual methods of treatment, a mastoidectomy was recommended.

Radical mastoidectomy revealed a partially differentiated squamous cell carcinoma of the right ear. Deep x-ray therapy, radon packs and radon capsules were ineffective in impeding the spread of the malignancy.

Approximately three months following her initial visit the patient complained of such severe shooting pain in the right ear and temporomandibular joint, as well as radiation of the pain to the head that the Department of Neurosurgery was called in consultation regarding measures to relieve this discomfort. At this time x-ray examination demonstrated involvement of the right temporomandibular joint as well as erosion of the cranial vault.

Associated with the pain was an increasing degree of anxiety and tension. These factors necessitated larger doses of sedation, so that neuropsychiatric consultation was also requested relative to the feasibility of prefrontal lobotomy. The extensive involvement of the malignant process created certain technical problems that rendered nerve section or intracranial tractotomy extremely difficult. Because of these complications and symptoms, a decision was reached after thorough discussion of the problem with the patient's family, to carry out lobotomy.

Bilateral prefrontal lobotomy was performed (W. James Gardner, M.D.) through burr holes located 3 cm. behind the outer canthus and 6 cm. above the zygoma.

The day following operation, the patient was apathetic, incontinent, manifested no anxiety or concern over her condition and although she admitted awareness of pain when questioned directly, did not ask for sedatives. This basic pattern existed at the time of hospital discharge sixteen days postoperatively.

Six weeks after bilateral lobotomy she was still apathetic (however, less so than immediately after operation), responded only when spoken to, expressed no complaints and when questioned directly concerning pain, acknowledged none. The anxiety and tension present prior to lobotomy were entirely absent.

The patient's daughter believed that the procedure had been justified even though the nursing problem was intensified. Clinically this operation was considered successful.

Case 2. Contralateral Postherpetic Neuralgia

A 65-year-old white man was first seen at the Cleveland Clinic on July 16, 1945 with the complaint of "terrific pain in, behind, and above the right eye" which had first caused him distress on February 9, 1945 and was described as severe, constant, sharp and burning. The next day his physician advised hot applications which were followed by blisters on the right side of the face in the distribution of the ophthalmic branch of the fifth cranial nerve. Four days after the diagnosis of glaucoma was made an operation was performed on the right eye. He was disoriented and confused for three days, postoperatively. On February 22, the right eye was removed. After enucleation the patient immediately experienced pain in the right orbit, as well as in the right forehead up to the hairline. The forehead was also described as feeling numb. The pain was paroxysmal in nature and often lasted as long as ten days. He was never free of pain for more than two to three days at a time. There was no visual disturbance preceding the onset of symptoms.

Physical examination on July 16, 1945 demonstrated a questionable hypalgesia in the first and third divisions of the right trigeminal nerve. A procaine hydrochloride injection of the right supraorbital nerve gave relief from pain for a week.

A subsequent alcohol injection of the supraorbital nerve did not relieve the pain but did anesthetize the forehead. A trial on x-ray therapy and the administration of sodium cacodylate was also valueless.

On September 21, 1945, the right greater superficial petrosal nerve was sectioned and at the same time the middle meningeal artery was ligated. These procedures failed to relieve the pain as did section of the sensory root of the right trigeminal nerve five days later. Subsequent stellate ganglion injections and excision failed to alleviate his discomfort.

Doctors Gardner and Karnosh were of the opinion that the patient's pain was probably due to preherpetic tension which finally broke out in a true herpetic crisis in August or September 1945. In view of the history outlined, the premise was accepted that discomfort was central in origin.

A unilateral prefrontal left lobotomy (W. James Gardner, M.D.) was carried out on October 28, 1946. This operation was performed under direct observation through an opening 2.5 cm. in diameter located one inch anterior to the coronal suture in the pupillary line to the left of the sagittal suture. The wound was covered with a tantalum plate 4 cm. square. For four to five days the patient was relatively free of pain but was confused, disoriented, and manifested a mild pyrexia.

One month later he was experiencing less pain and using less sedation. Five months following unilateral lobotomy the pain was again as severe as ever. The only favorable com-

ment was that he was slightly less depressed. The patient and his family refused right prefrontal lobotomy.

The case demonstrates a failure from unilateral prefrontal lobotomy. Unilateral prefrontal lobotomy, however, has proved to be effective in some instances.

Case 3. Neuralgia, Chronic Depression and Drug Dependence

A white woman, 52 years of age, had been seen at the Cleveland Clinic on numerous occasions throughout the past twenty-three years for a variety of disorders. The chief problems were hyperthyroidism, for which she had undergone a thyroidectomy in 1924, hypochromic anemia, postherpetic neuralgia involving the left trigeminal nerve with subsequent intracranial section of the sensory root of the 5th cranial nerve, and a mixed depression of long standing.

Although complete anesthesia in the area of the left trigeminal nerve had existed since the section in January, 1944, she continued to complain of "misery" and pressure in the head, with severe intractable pain in the left temple.

In September 1944, she was given electroshock therapy without any permanent relief.

At the time of the last admission to the Clinic Hospital on April 1, 1947, she proffered the same complaints as recorded previously, and in addition, was found to be emaciated with evidence of deficiency disease. The patient's husband stated that she had been taking increasing amounts of barbituates for the past several years.

A bilateral prefrontal lobotomy was performed on April 10, 1947 (A. T. Bunts, M.D.). Under local anesthesia a short scalp incision was made 1.5 inches to either side of the midline, and the middle of each incision was located about 3.5 inches posterior to the supraorbital ridge. The periosteum was elevated from the frontal bone on the right side, and a drill-hole made through the skull at a point 3.5 inches behind the supraorbital ridge. The bony drill-hole was enlarged with rongeurs to the size of a quarter. The dura was opened with stellate incisions. The surface of the brain was treated with the electrocoagulator, and an incision about 1 inch long made through the cortex. By using the aspirator, the septum elevator, and flat, narrow retractors, the white matter of the frontal lobe was divided transversely in a direction parallel with the coronal suture. The anterior horn of the right ventricle was entered, and the operation then carried somewhat anterior to the ventricle.

At the end of the procedure the patient stated that she was free from her former pain. On the left side a similar operation was performed. In this instance the operation was carried down to the floor of the anterior fossa of the skull, the ventricle was not entered on the left side. It is probable that the upper inner quadrant and upper outer quadrant were not completely sectioned on either side. The patient asserted that she was undisturbed by the postherpetic neuralgia formerly present in the left frontotemporal area. It was not possible to evaluate her response accurately at the immediate postoperative period because she had received ¼ gr. of morphine and 3 gr. of nembutal several hours previously. Her response to questions was accurate, and she seemed to show no definite psychologic change except for a certain loquacity which had not been present before.

For several hours after the operation she was quiet, responded only when spoken to, and although there was some pain present, she appeared to suffer no discomfort and requested no medication. (Prior to operation she had made frequent requests for sedatives.)

The patient was next seen in June 1947 and appeared to have improved physically. Her appetite had improved, she had gained weight and no longer relied upon sedative drugs. She admitted that pain persisted but did not trouble her.

In November 1948 she was re-examined and appeared to have acquired poise and good spirits. She profferred no complaints. She had gained 25 pounds and normal appetite and sleep rhythm had been restored. Anesthesia in the area of the left trigeminal nerve was still present but the patient no longer complained of pain and the necessity for sedatives.

Psychometric studies done on the patient, November 11, 1948 revealed a full scale I. Q. of 81. Her education had stopped at the eighth grade and the vocabulary score was consistent with her initial limited endowment.

Verbal tests revealed that the patient's thought faculty functioned in extremely low, concrete terms, but that she was attempting to use her knowledge effectively in dealing with

reality problems. Although she was able to maintain voluntary attention, she had difficulty in concentrating for any length of time. On two of three performance items requiring visual-motor coordination, the patient received her highest scores. In the third, a test of both writing and ocular shifts as well as a learning situation, the patient evidenced psychomotor retardation. She was lethargically cooperative and recognized her failure without sensitivity.

The electroencephalographic report done on November 11, 1948 showed an abnormal organic type of record with maximum changes in the frontal and right parietal regions.

The case described represents the most satisfactory result in the current series. It is entirely possible that her greatest difficulty was in the psychogenic sphere. Repeated references have been made regarding the encouraging results obtained in situations where anxiety and depression predominate.

Case 4. Pain from Recurrent Osteochondromas

A white man, age 44, was first seen at the Cleveland Clinic in March 1938. He had a mass above the right hip (above the right ilium on the anterolateral aspect) of one month's duration. Except for slight pain in the right groin and area about the tumor and mild stiffness of the right leg and thigh, the present illness was uneventful.

Physical examination revealed an atrophic left testis (post mumps), and a firm, non-movable, non-tender mass measuring approximately 9 by 6 cm. running parallel to the right iliac crest and attached to the inner aspect of the flare of the ilium above the spine. X-ray of the right ilium at the time of the first visit revealed a large tumor. Considerable bone production with some bone destruction was noted.

On March 30, 1938 the tumor mass was removed from the inner surface of the right ilium. The pathologic diagnosis was osteochondroma of the right ilium. The postoperative course was uneventful and in the ensuing months the patient gained weight and expressed few complaints.

Because of recurrence of the tumor a second operation was performed on April 22, 1940. At this time he complained of pain radiating from the ilium into the lateral aspect of the right thigh. Subsequent removals were performed in August 1942, December 1943, July 1944 and June 1945.

In September 1946, the patient returned complaining of severe pain in the right leg. At this time Dr. Gardner, advised unilateral cordotomy and this was carried out at the level of D-1 on the left, on October 14, 1946. This procedure relieved the discomfort to a great extent in the right leg but shortly thereafter he experienced dull aching pain in the left sacro-iliac region which grew progressively worse, was aggravated by heat and when lying down, but was relieved by cold. By October 26, 1946 there was analgesia up to the level of D-10 on the right, but in spite of this there was some discomfort during manipulation of the right leg.

By the summer of 1947, the patient was taking increasing amounts of morphine sulphate, codeine and dilaudid to relieve the discomfort. He was readmitted to the Clinic Hospital on August 17, 1947 because of shooting pains down the anterior aspects of both thighs, accentuated on the right. There was also pain in the left hip. At this time the question of bilateral cordotomy versus bilateral prefrontal lobotomy was discussed. Inasmuch as the patient was addicted to drugs, was experiencing increasing amounts of pain, swelling of both feet due to mechanical factors, and faced the prospect of increasing anxiety and apprehension, bilateral prefrontal lobotomy was chosen to relieve his discomfort.

Lobotomy was performed on August 20, 1947 (W. James Gardner, M.D.). The following day he was calm, denied having pain and voided in bed without requesting a urinal. By August 25, 1947 it was noted that (1) he no longer smoked or asked for cigarettes, whereas previously he had been a heavy smoker; (2) he would eat any amount of food given him; (3) he was disoriented as to time and place, but did recognize his wife and (4) he expressed no complaints whatsoever. At the time of his discharge from the hospital on August 30, 1947 there had been definite improvement in bowel and bladder control and the patient had begun to shave himself. The pain was almost completely relieved but he obviously lacked his accustomed drive and ambition.

Unfortunately this patient was never re-examined, but excerpts from his wife's letters describe the results of this form of therapy:

October 1, 1947: "He has gained six pounds, appetite is good and he sleeps well. He is taking NO medicine.

There has been progress in his mental condition. His memory is not too accurate about some things, yet, about others is exceptionally good. He is able to converse as well as he ever did and his reasoning powers are good. For example, he plays a difficult game of solitaire and can figure a mathematical problem rapidly. (These are things he excelled in prior to the operation.) He is not interested in reading as he once was and seldom discusses business matters or current events. His attitude is relaxed about all problems.

These are the good things and, as they outnumber the bad, I am deeply grateful and am convinced that this operation was helpful.

On the other hand, he has experienced pain, constipation, bed wetting and procrastination. Three weeks ago he became conscious of pain and there has been much of it. However, he does not seem to have any bad effect from it. Some days are worse than others in this respect.

Concerning the bed wetting, he is not aware of it as it only happens while he is sleeping and, when he awakens and realizes what has happened, it is a source of unhappy concern to him. He performs toilet functions normally during the daytime. I think this is because of this new and bad habit of putting things off. He has the most advanced case of "I'll do it in a minute" that I have ever seen. For example, he will plan to do some chore, then will sit for hours without starting. I have seen him sit in his room for a half day with his shaving kit in his hand, then walk into the bathroom and remain three hours. Or, he will plan to go someplace, perhaps invite a guest, then fail to be ready for the appointment for hours. My husband was always a punctual and conscientious person and I sincerely hope this is a temporary phase of his recovery.

He enjoys going out and we have visited friends, gone to the movies and attended several sports events. He is able to walk better than he could prior to the operation and his foot and ankle swell but slightly each day."

October 14, 1947. "You asked if he mentions his pain spontaneously. For three weeks after the operation he complained of none, but suddenly he became aware of pain and since that time has mentioned it. In fact, he talks about it a great deal. One of your associates told me that he might speak of his pain but I had the impression that it would not really bother him. I believe that it does bother him for he can sleep in only one position and, when he is up, he moves from chair to chair and changes his position frequently which he says gives him relief.

His appearance is greatly improved. His appetite is excellent and he sleeps well in spite of the pain which he says bothers him during his waking hours. Altogether, there is a remarkable improvement."

January 8, 1948. "For the past three months he has been fair. He has recovered completely from the effects of the last operation.

The tumor has increased greatly in size and he has become lame. In addition to this he is in pain most of the time. This causes him to lose sleep and to accomplish little work.

Some time ago he began taking a drink of whiskey which he found relaxed the nerves "jumping in his leg." As time went on he drank more and more, until now, he drinks a fifth of whiskey in twenty-four hours. The amazing thing to me is that this whiskey does not make him drunk. He simply drinks it by the glassful and there is no apparent effect except that he can sleep after so long a time. So far, it has not affected his appetite, which remains good. He does not particularly like whiskey and could and would stop drinking immediately if relieved of the pain."

On January 20, 1948, his attending physician wrote the following comments: "He has had some recurrence of his discomfort, although he states that it is not at all severe and not the same as prior to his lobotomy. He describes this as "nerve twitching" and pain which lasts momentarily and is referred down over the right thigh. This comes on particularly after he retires. He is accustomed to drinking approximately a fifth of whiskey, which he states helps him to go to sleep but he does not believe that it actually diminishes his pain. He states that he has consumed considerably more alcohol since his lobotomy than prior to

it and has not noticed any particular effect of the alcohol. He believes that his tolerance is as good for alcohol now as it was prior to his operation.

On examination I find further encroachment of the tumor into the tissues of the right thigh as well as the right lower quadrant of his abdomen."

A second letter from the attending physician said. "I have seen the patient on several occasions recently. He is failing rapidly and although not having a great deal of pain is apparently approaching the terminal stages of his condition. For a time he exhibited evidences of an intestinal obstruction. However, this has not been evident recently. He is gradually growing weaker and has had several attacks not unlike the petit mal of epileptic seizures."

The patient died on March 15, 1948.

While the results of lobotomy were not altogether satisfactory in this case a moderate degree of success was achieved in alleviating his pain. The relief of anxiety and apprehension and lack of necessity for sedatives were most satisfactory.

Case 5. Malignancy of the Kidney with Metastases

A 62-year-old white woman was first observed in December 1948, because of severe pain in the left hip, thigh, and abdomen, of approximately eight to ten months' duration. The patient was bedridden because of the extreme pain and weakness and required large doses of morphine sulphate, empirin compound and codeine to gain relief.

The diagnosis of carcinoma of the left kidney with metastasis to the left ilium and spine was made elsewhere.

In view of the apparent involvement of the spine with root irritation, cordotomy was decided against because of the likelihood of producing paralysis.

Bilateral transorbital prefrontal lobotomy (W. James Gardner, M.D.) was performed and immediately postoperatively the patient stated that she had much less pain. However, within four or five days it was apparent that this procedure was not effective since the patient complained of excruciating pain in the left leg and epigastrium. By this time there was also definite evidence of involvement of the spine, an increasing demand for sedation, a moderate degree of depression and considerable fear and anxiety.

Subsequently, standard prefrontal lobotomy (W. James Gardner, M.D.) was performed in two stages. The operations were carried out through openings in the line of the coronal sutures placed approximately 2 cm. laterally from the midline of the skull. Both openings were covered by a tantalum plate.

Although sufficient time has not elapsed to accurately evaluate the results, the immediate postoperative course definitely revealed less anxiety and depression and decrease in the amount of pain.

This case demonstrates that the more minimal procedure of transorbital lobotomy was insufficient to produce the desired effect. It has been estimated that this method is effective in approximately 30 per cent of cases.

Summary

Standard lobotomy was found to be satisfactory in 2 cases (case 1, for intractable pain from carcinoma of the mastoid, and case 3, for postherpetic neuralgia, chronic depression and drug dependence). The same procedure was moderately successful in relieving the pain in two instances (case 4, for pain from recurrent osteochondroma and case 5, for pain from malignancy of the kidney with metastases).

Transorbital lobotomy was ineffective for the relief of pain in 1 case (case 5, although the patient was subsequently relieved by standard lobotomy).

Unilateral lobotomy was unsuccessful in relieving the discomfort of contralateral postherpetic neuralgia in 1 case (case 2).

Conclusions

Prefrontal lobotomy is a valuable therapeutic procedure in selected cases. It is our opinion that it should not be employed until other more conservative methods of treatment have failed to produce the desired results. Lobotomy is frequently more desirable than the traumatizing technics of cordotomy and tractotomy especially when the basic condition is complicated by extreme anxiety and excessive dependence on drugs.

Lobotomy will not eliminate pain but it will alter the individual's reaction to discomfort. Watts and Freeman have aptly concluded that "pain may be present but when divorced from its implications—the threat to the patient's security and fear of disability and death—it then becomes bearable and may be accepted with fortitude."

References

1. Moniz and Lima, cited by Watts and Freeman.[2]
2. Watts, J. W., and Freeman, W.: Psychosurgery for relief of unbearable pain. J. Internat. Coll. Surgeons **9**:679-683 (Nov.-Dec.) 1946.

MEDIASTINAL TUMORS

DONALD B. EFFLER, M.D.
Department of Thoracic Surgery

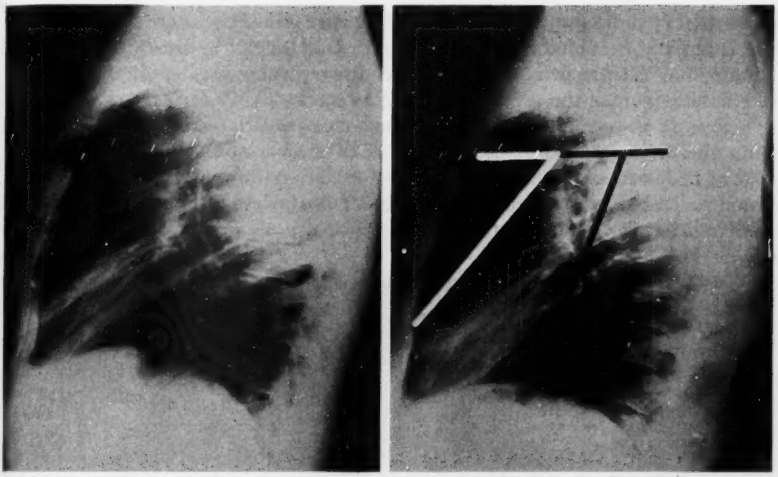
UNTIL recent years the mediastinum was considered as a "No Man's Land" insofar as elective surgery was concerned. Except for the extirpation of the substernal goiters from the superior mediastinum, little else was attempted in this region. The collection of mediastinal tumors was left almost entirely to the pathologist as most of these entities were discovered at postmortem examination. As roentgen examination of the chest increased in popularity, however, the tumors were detected more frequently during life and the opportunity for clinical study became a frequent occurrence. With the development of improved surgical technics in the past decade, the third phase of study and treatment of mediastinal tumors has come into being. Early detection by roentgenography and early exploration of the mediastinum have combined to improve the clinical management and the prognosis of the patient with mediastinal neoplasm. The low morbidity and mortality of exploratory thoracotomy make this operation a safe method of diagnosis and treatment. Prolonged clinical observation is no longer a justifiable procedure in the management of these patients.

"The mediastinum is the space left in the median line of the chest by the non-approximation of the two pleurae (Gray's Anatomy)." Classically, this space is subdivided into four compartments, all of which are surgically accessible (fig. 1). An imaginary plane extending anteriorly from the fourth thoracic vertebra to the articulation between the manubrium and the sternum forms the lower border of the superior mediastinum. This corresponds roughly with upper limits of the pericardium. Below this plane and above the diaphragm are the anterior, middle and posterior mediastinal compartments. If the pericardial sac and its contents are considered the middle mediastinum, the anatomic features of the anterior and posterior spaces may be easily recalled. A simple classification of these four compartments and their normal contents follows.

Superior Mediastinum

1. Aortic Arch and Great Vessels
2. Innominate Veins and Superior Vena Cava
3. Trachea, Esophagus and Thoracic Duct
4. Phrenic N., Vagi, and L. Recurrent Nerve
5. Thymus

Posterior Mediastinum	Middle Mediastinum	Anterior Mediastinum
1. Descending Aorta	1. Pericardial Sac and Contents	1. Lymph Glands
2. Azygos and Hemiazygos V.	2. Phrenic Nerves	2. Fat and Areolar Tissue
3. Esophagus		3. Thymus
4. Thoracic Duct		
5. Vagi		
6. Sympathetic and Splanchnic N.		



(a) (b)

FIG. 1. The mediastinal compartments are best demonstrated radiographically by lateral projection of the chest. (a) Shows a normal adult male thorax; (b) contains the arbitrary boundaries of the mediastinal compartments.

In the study of anatomical charts and in cadaver dissection one may be led to regard the mediastinal space as an inert area whose only importance depends on the structures within its boundaries. Actually this is not true. The motion of the heart plus the ceaseless excursions of respiration contribute to the constant flux in the size and the positions of these compartments. During life the entire mediastinum is subject to numerous vectors of force from the cardiorespiratory mechanism. The importance of these mediastinal mechanics in the dissemination of local infection or malignancy is unknown. Conversely, however, it is not difficult to anticipate the mechanical problems presented by a firm tumor in this area which is encased by the unyielding bony thorax.

Tumors of the mediastinum occur at all ages; however, they are more frequently seen before the sixth decade. There does not seem to be a general pattern of sex incidence. The ratio of benign and malignant features depends on the origin or cell type of the neoplasm and not on its association with the mediastinum. The most striking feature of mediastinal tumors is their tendency to conform to a pattern of location. The recognition of this "geographical" tendency aids in our clinical approach to diagnosis and management. For this reason, many writers have tended to classify these neoplasms by their anatomic site rather than histopathologic type.

Lymphatic Tumors. This group includes the lymphomas, lymphosarcoma, Hodgkin's disease, lymphocytoma, etc. These tumors of lymphatic origin occur most commonly in the anterior mediastinum[1] and are probably the most common tumors in this site. They vary considerably in their degree of

malignancy; some are locally invasive and fast-growing whereas occasionally there might be complete encapsulation.[2] In Hodgkin's disease, the mediastinum may be the primary site of the disease although it probably is more often only a part of the general picture.[3] Even Hodgkin's disease may occasionally present an encapsulated mediastinal mass that is amenable to excision; a number of such cases are reported.[4] With the variation manifested by lymphatic neoplasms, one would expect a variation in the symptom complex. Some patients have no subjective symptoms but are discovered on accidental radiologic examination. Others have evidence of weight loss, mediastinal

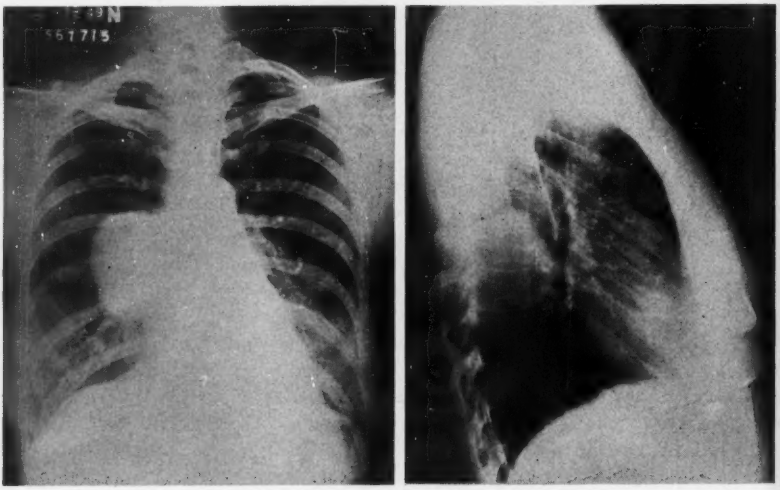


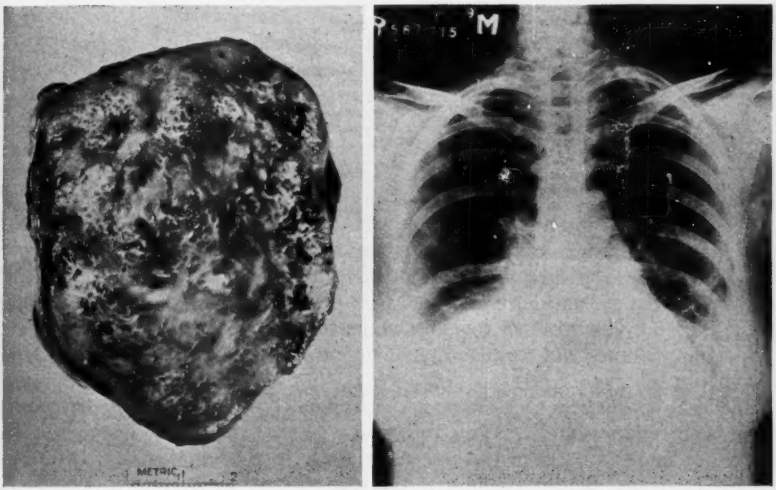
FIG. 2. Case 1. Routine PA and lateral projections demonstrate a well circumscribed mass in the right posterior mediastinum. The patient, a 49 year old white woman, had no symptoms of an intrathoracic tumor. The position and contour of the neoplasm are typical of a neurogenic mediastinal tumor.

compression, hemoptysis and dyspnea. The course of the disease may be rapid or slow; in occasional cases there may be prolonged remissions. The variations in cell type and the tumor characteristics of these lymphatic neoplasms account for the inconsistency of their clinical and roentgenographic appearance.

Dermoid Cysts and Teratoid Tumors. These tumors are seen most commonly in the anterior mediastinum and with almost the same incidence as the neoplasms of lymphatic origin.[1] Dermoid cysts are said to have their origin from epidermal tissue whereas the teratomas arise from all three of the germinal layers.[5] Clinically, the teratoma seems to show a much greater incidence of malignancy than the dermoid cyst. The incidence of malignancy in this group of tumors has been variously reported as being between 13 per cent and 40 per cent.[6,7] Whereas there does not appear to be a sex predilection, these tumors

are seen more commonly in youth and rarely after the age of fifty. The treatment of this group of tumors is surgical unless there is malignant invasion of neighboring structures. Roentgen therapy is usually of no value.[6]

Thymic Tumors. Tumors of the thymus are almost always found in the anterior mediastinum. These lesions are not common. Interest in thymic neoplasms was stimulated in 1917 by Bell, who reported ten tumors of the thymus in 56 patients who had died of myasthenia gravis.[8] Since that time a number of reports on thymectomy for myasthenia gravis have been published. In the majority of cases hyperplasia of the gland was demonstrated; however, primary



(a) (b)

FIG. 3. Case 1. (a) Shows the cut section of tumor demonstrated in figure 2. Microscopic diagnosis is: neurilemmoma, benign; (b) shows a reproduction of the postoperative roentgenogram taken on the sixth postoperative day.

tumors were present in a variable percentage of cases. These tumors are usually benign but a wide variety of malignancy has been described.[9]

Diagnosis of thymic tumors is usually based on the location and roentgen findings. A lateral projection of the chest may be of considerable value in demonstrating the mass.[10]

Bronchiogenic Cysts. These cystic masses may be located at any point in relation to the tracheobronchial tree. In the mediastinum, however, the common location appears to be in the superior mediastinum near the tracheal bifurcation. This may appear anteriorly or posteriorly. Bronchiogenic cysts differ greatly in their growth and their microscopic appearance. The tumors, however, are usually round or ovoid in shape and frequently are attached to a bronchus or the trachea by a stalk. The cyst may be solid or may be thin-

walled and contain clear fluid. On microscopic examination the cysts may contain any or all of the tissues normally present in the tracheobronchial tree. Bronchiogenic cysts may produce no symptoms of any kind and may appear to be completely innocuous in character. However, they frequently are subject to secondary infection and produce the clinical picture of a bizarre type of pneumonitis. Blades suggests that so-called carcinoma of the mediastinum may originate in bronchiogenic cysts since these tumors are developmentally and histologically related to the teratoid tumors. The treatment of bronchiogenic cysts is surgical; excision is usually not difficult if no infection is present (figs. 2 and 3).

Neurogenic Tumors. The primary nerve tumors arising in the thorax are almost always seen in the posterior mediastinum.[1,11] Their radiographic appearance varies. They may appear to be round or lobulated but the principal characteristic of the tumor is the position in the posterior mediastinum. Usually these neoplasms are asymptomatic; however, they have been reported to produce Horner's syndrome when sympathetic chain involvement is present.[12] Frequently these neoplasms are discovered on an incidental roentgenogram of the chest. Primary nerve tumors may arise from any of the nerve elements found in the mediastinum but most commonly from the sympathetic chain, intercostal nerves and, less commonly, from the vagus or phrenic nerves. Whereas the variety of these primary nerve tumors is great, since they may arise from the various embryonal nerve elements, from the clinical standpoint they may be grouped together under "primary nerve tumors" as their clinical appearance and surgical management are essentially the same regardless of the cell type.

Several large series of primary nerve tumors of the posterior mediastinum have been reported and it is interesting to note that there is a relatively high degree of malignancy seen in these neoplasms. In the series of 105 cases reported by Kent, Blades, Valle and Graham, 37 per cent were found to be malignant in character [11](figs. 4 and 5).

The suggested treatment of primary nerve tumors of the posterior mediastinum is surgical. In view of the high degree of malignancy in these mediastinal tumors, there seems to be little justification in "watchful waiting" when the patient has not had any localizing symptoms. No benefit can be expected from radiation therapy in the treatment of nerve tumors of the thorax. Unless the nerve tumor has already undergone malignant degeneration, surgical excision is a reasonably safe procedure accompanied by a high rate of cure.

Pericardial Cysts. These benign tumors usually arise from the parietal pericardium and appear on roentgen examination to be in the anterior portion of the mediastinum. It is felt that they represent an anomalous development of the pericardium and, as such, are to be classified as "embryonic developmental defects."[13] There does not appear to be any characteristic roentgenologic findings to differentiate them from other types of mediastinal tumors. On gross examination, they usually are thin-walled structures and are adherent to the parietal pericardium. Surgical extirpation appears to be the only manner of establishing the diagnosis of this benign tumor.[4]

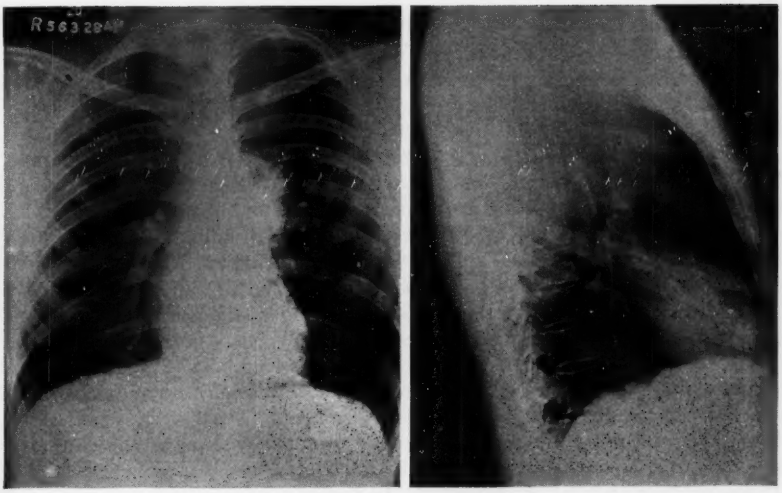


FIG. 4. Routine PA and lateral projections of the thorax demonstrating a mass in the anterior mediastinum in white male patient, aged 30.

Gastro-enterogenous Cysts. These cysts represent another of the embryonal defects occurring in the thorax. In such cases the cysts are usually lined with intestinal mucosa that may have the characteristics of stomach or small bowel. It has been suggested that they represent pinching off of buds or diverticula from the foregut[14] and/or intrathoracic vestiges of the omphalomesenteric duct. In addition to appearing characteristically in the posterior mediastinum,[14] they are more frequently seen on the right side than the left. These tumors usually are discovered early in life, frequently in early infancy. Those tumors with gastric mucosa have been reported to contain acid and to produce peptic ulcer.

Miscellaneous Tumors. In addition to those neoplasms previously described, there are many types of tumors which have been reported in the mediastinum; however, none of these is common nor are they characteristic in their appearance or position. Such tumors as xanthomas, hemangiomas, lymphangiomas, echinococcal cysts, tuberculomas, parathyroid adenomas and sarcoid occasionally reported as an operative or postmortem finding. Actually, the variety of expected neoplasms which might be present in the mediastinum seems almost unlimited. However, in the broad sense, there appears to be a somewhat orderly pattern in the type and the localization of the mediastinal tumors. Whereas diagnosis cannot be made except by actual tissue biopsy, a fair estimate can be made by the location of the tumor and the roentgen and clinical observations.

Treatment

Much has been written about the management of various types of mediastinal tumors. There appear to be approximately four major possibilities of treatment: (1) observation; (2) roentgen therapy; (3) chemotherapy; (4) and exploratory thoracotomy.

The dangers of clinical observation of a mediastinal tumor are apparent. Whereas the term "watchful waiting" has been used since the dark ages, there is still a good deal of question as to how long one should wait and just exactly what should be watched. Observation of a mediastinal tumor implies the complete satisfaction of the clinician that he is dealing with a benign lesion. Experience has shown that it is impossible to determine the benignity of a mediastinal tumor on x-ray and clinical observations alone. Hence there seems little reason to delay treatment.

Roentgen therapy in mediastinal tumors has little value except in the tumors of lymphatic origin. There is no question that it is the most beneficial form of therapy in those lymphoid tumors that are bilateral or involve surrounding tissue. Occasionally a lymphatic tumor is well encapsulated and is amenable to resection; this property is usually discovered only at the time of thoracotomy and may be difficult to predict.

The use of roentgen therapy as an aid in diagnosis must also be considered. In good hands, the use of the so-called "test dose irradiation" may be of extreme importance. In those tumors of the anterior mediastinum where lymphatic origin is suspected, a test dose of roentgen therapy may cause the neoplasm to promptly diminish in size. According to Friedman[4] the initial test dose should be approximately 750 r. delivered to the center of the tumor. Approximately one-third of malignant lymphomas will require, however, 1500 r. to affect the tumor. Any decrease in size should be demonstrable within one month's time.

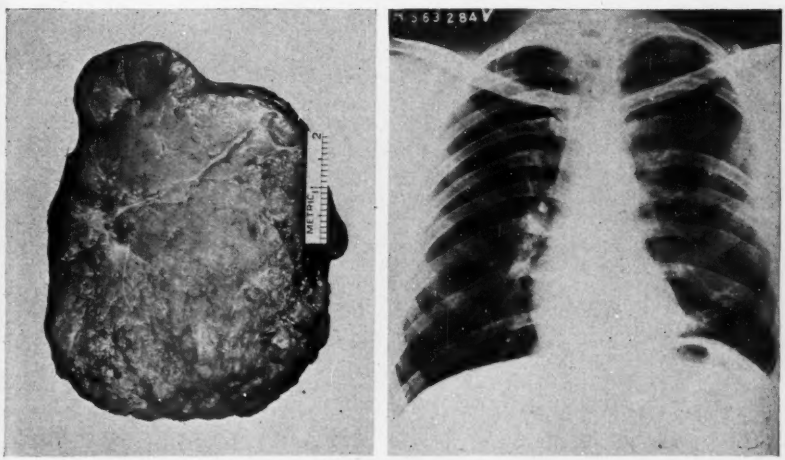
It must be kept in mind by those who would employ radiation therapy without justification that this is not an innocuous form of treatment. The deleterious effects of prolonged, ineffectual radiation therapy cannot be estimated. The length of time involved in a course of roentgen therapy may be sufficient to permit an operable malignant tumor to go beyond the range of operability. The hazards of radiation fibrosis to skin and intrathoracic tissues must also be kept in mind. As a general rule, roentgen therapy in the treatment of mediastinal tumors must be confined to those of suspected lymphatic origin.

The use of chemotherapy in the treatment of mediastinal tumors is of questionable value. The antibiotics have no place except in the unusual cases such as certain types of bronchogenic cysts whose contents undergo secondary infection. Nitrogen mustard is undergoing clinical trial at the present time and, like radiation therapy, its use is being confined to the tumors of lymphatic origin.

It has been stated by Blades[4] that the danger of exploration of the mediastinum is trivial provided qualified anesthetists and surgeons are available and that the patient is in reasonably good general condition. In light of our

present knowledge and technics, it would seem that this statement is easily supported by the present low morbidity and mortality associated with exploration of the thorax. The philosophy of therapy in mediastinal tumors is gradually changing for more frequent use of exploratory thoracotomy following diagnosis of a mediastinal tumor. As the majority of neoplasms in this area are probably benign and asymptomatic, there is still a tendency on the part of many clinicians to procrastinate in the definitive treatment of these tumors. It must be kept in mind, however, that when operation is delayed until the signs and symptoms of chest pain, enlargement of the tumor mass and weight loss have become apparent, the opportunity for successful removal of the lesion will usually have been lost.

That the postoperative morbidity and mortality of exploratory thoracotomy for mediastinal tumors are low is attested by the results of the Army General Hospital as reported by Blades. In a total of 114 exploratory operations to determine the nature of a mediastinal tumor, there were no deaths in the series that could be attributed to the operation. In those patients upon whom only exploration and biopsy were performed, there were no postoperative complications. In the patients who had actual removal of their tumors, there were 3 cases of suppurative pleuritis that healed promptly following adequate drainage. It must be borne in mind that the excellent results were not obtained by one surgeon or a small selected group, but by the combined efforts of five different hospitals with well trained surgeons and anesthetists.



(a) (b)

FIG. 5. (a) Cut section of tumor removed surgically. Microscopic examination revealed no evidence of malignancy. Diagnosis: sympathogonioma; (b) postoperative roentgenogram one month after thoracotomy.

Summary and Conclusions

Undoubtedly, the increased use of roentgen examination of the thorax will uncover an increasing number of cases of mediastinal tumors in the future. The majority of these patients will probably be completely devoid of symptoms, especially in the younger age groups. Whereas the location of the tumor mass will give some clue as to its presumptive diagnosis, exploration of the mediastinum to expose the neoplasm is still the only means available for accurate diagnosis and proper therapy in a large percentage of cases. The hazardous procedure of "watchful waiting" has no place in the clinical management of mediastinal tumors. Surgical intervention in cases of asymptomatic mediastinal tumor before the onset of clinical manifestation is the preferred treatment.

References

1. Blades, B.: Relative frequency and site of predilection of intrathoracic tumors. Am J. Surg. **54**:139-148 (Oct.) 1941.
2. Effler, D. B., Blades, B., and Marks, E.: Problem of solitary lung tumors. Surgery **24**: 917-928 (Dec.) 1948.
3. Heuer, G. J., and Andrus, W. De W.: Surgery of mediastinal tumors. Am. J. Surg. **50**:146-224 (Oct.) 1940.
4. Blades, B.: Penicillin as adjunct to surgical treatment of acute and chronic empyemas. Tr. South. S. A. (1944) **57**:288-295, 1945.
5. Hedblom, C. A.: Intrathoracic dermoid cysts and teratomata with report of 6 personal cases and 185 cases collected from literature. J. Thoracic Surg. **3**:22-49 (Oct.) 1933.
6. Rusby, N. L.: Dermoid cysts and teratomata of mediastinum; review. J. Thoracic Surg. **13**:169-222 (June) 1944.
7. Harrington, S. W.: Surgical treatment in 16 cases of anterior mediastinal teratoid tumors; one complete report of case. J. Thoracic Surg. **7**:191-205 (Dec.) 1937.
8. Bell, cited by Thompson, J. V.: Collective review; mediastinal tumors and cysts. Internat. Abstr. Surg. **84**:195-221, 1947 in Surg., Gynec. and Obst. (March) 1947.
9. Andrus, W. De W., and Foot, N. C.: Report of large thymic tumor successfully removed by operation. J. Thoracic Surg. **6**:648-659 (Aug.) 1937.
10. Blalock, A.: Thymectomy in treatment of myasthenia gravis. J. Thoracic Surg. **13**:316-339 (Aug.) 1944.
11. Kent, E. M., Blades, B., Valle, A. R., and Graham, E. A.: Intrathoracic neurogenic tumors. J. Thoracic Surg. **13**:116-161 (April) 1944.
12. Andrus, W. DeW., and Heuer, G. J.: Surgical treatment of tumors of mediastinum. Surg., Gynec. and Obst. **63**:469-482 (Oct.) 1936.
13. Freedlander, S. O., and Gebauer, P. W.: Disease of aberrant intrathoracic lung tissue. J. Thoracic Surg. **8**:581-597 (Aug.) 1939.
14. Carlson, H. A.: Congenital cysts of mediastinum; report of 3 cases including gastric cyst. J. Thoracic Surg. **12**:376-393 (April) 1943.

APPOINTMENTS

Dr. Eric Bell, Jr., has been appointed to the staff in the Department of Neuropsychiatry. Dr. Bell graduated from Vanderbilt University in 1940. He attended Vanderbilt School of Medicine and received the M.D. degree from that institution in 1943. Following a rotating internship at the City Hospital in Cleveland, Dr. Bell served a Junior Assistant Residency in Neuropsychiatry at the same institution until September, 1944. He then served in the Medical Corp of the U. S. Naval Reserve for two years, returning to the Cleveland Clinic to complete his training.

Dr. Bell has been certified by the American Board of Psychiatry and Neurology in the field of psychiatry and has published several articles in the medical literature. He is a member of the American Psychiatric Association, Cleveland Society of Neurology and Psychiatry, the American Federation for Clinical Research, and several other medical organizations.

Mr. Maynard H. Collier has been appointed Administrator of the Cleveland Clinic Hospital. He succeeds Miss Abbie I. Porter, who has retired after 25 years of service. A native of Greater Cleveland, Mr. Collier graduated from Ohio Wesleyan University in 1931. After working in the Credit and Estate Departments of the Cleveland Trust Company, he joined Card, Palmer, and Sibbison, a firm of Cleveland public accountants and tax consultants, and had been associated with the Cleveland Clinic for about a year prior to his appointment as Hospital Administrator.

NOTICE

The camp for diabetic children, Ho-Mita-Koda, situated in a wooded area near Newbury, Ohio, about 25 miles east of Cleveland will be open again this year. This camp, which is operated as a nonprofit institution, is especially designed to serve the needs of both boys and girls between 6 and 16 who have diabetes. A resident physician, nurses, and dietitians are in attendance. Camp activities include swimming, hiking, tennis, archery, and handicrafts. The camp will be open for two periods of one month each, the first period beginning June 26.

The standard fee for the camp is $150 per period. Inquiries concerning placing diabetic children in this camp may be sent to the Director, Mr. Byron Williams, R. F. D. No. 2, Chagrin Falls, Ohio.

MODERN TRENDS IN DIABETES*

HENRY T. RICKETTS, M.D.
Associate Professor of Medicine, University of Chicago

UNTIL the last war, the incidence of diabetes was thought to be from one-half to seven-tenths per cent of the total population, and the total number of diabetics was supposed to be not greater than one million. In 1943, Dr. Blotner,[1] then a reserve officer in the army, examined some 45,000 inductees and found that among these relatively young men, in whom diabetes is less common than in older ages, the disease had an incidence of nearly one-half of 1 per cent. This aroused Dr. Blotner's suspicion that diabetes was more prevalent than any of us had heretofore recognized. Three years later he[2] was able to examine a larger group—some 69,000 inductees—and here with more careful methods and the more liberal use of blood sugars rather than urine sugars, an incidence of 1.1 per cent was found, again in this relatively young group of people. This implied more strongly than ever that in the population at large the number of diabetics must be considerably higher than formerly believed.

In 1947 this supposition was confirmed by a careful survey conducted by Drs. Wilkerson and Krall[3] of the U. S. Public Health Service, in Oxford, Massachusetts, appropriately enough the former home of Dr. Elliott P. Joslin. Among some 3500 people who were carefully examined there were 70 diabetics in this town of approximately 5,000 inhabitants and of these 40 had previously known they had the disease and 30 had not suspected it. This then is a ratio of almost one unknown diabetic for every one who was known. Thus, instead of a million diabetics in the United States there are probably nearer two million.

It is important to find them because by bringing them under early treatment, we hope to accomplish two things: we hope to prevent mild cases from becoming severe, and we hope to prevent the more severe cases from developing complications. Please note that in expressing this hope, we are implying that by proper treatment mild diabetes can be prevented from becoming severe and severe diabetics can be prevented from having complications. This implies careful regulation of the diabetic. If this were not so, there would hardly be any point in trying to find a million unknown diabetics. In the campaign to discover the million unknown cases, special emphasis is being placed on the obese person because about 80 per cent of people with diabetes acquire their disease while they are overweight. Attention is being paid particularly also to those with a family history of diabetes because there is a definite hereditary element in the disease. We are on the look-out for people over 40

*This paper is slightly abridged from a wire recording of a lecture given March 17 in connection with the Bunts Institute course on Diabetes.

because diabetes is predominantly, though by no means exclusively, a disease of the older age groups. The fourth category of special suspects are those who have had or are having an acute illness because acute illness often brings to light a latent diabetes.

Another development in the diabetes problem is the progress being made toward cracking the problem of what causes diabetes. Why do people get it and how do they get it? For a long time we were not even sure what organ was involved in the cause of diabetes. In the latter part of the last century Von Mering and Minkowski seemed to have settled that problem by discovering that if one took the pancreas out of a dog, the dog developed diabetes. This seemed to end at least for that time all controversy about the subject. Soon, however, it was found that patients with diseases of other parts of the body also got diabetes. Also there was a good deal of difficulty in demonstrating microscopically that the pancreas was really involved in many patients who had died after having nad diabetes for a long time. Both the anterior pituitary and the adrenal cortex have now been implicated as organs if not primarily responsible for diabetes, at least as important in its causation. One can produce permanent diabetes in animals by anterior pituitary substances without touching the pancreas directly.[4] One can also produce hyperglycemia and glycosuria in animals by injections of adrenal cortical extracts without operating upon the pancreas.[5,6] Furthermore, if diabetes is produced by taking out the pancreas, the disease can be alleviated—almost cured—by removing the anterior pituitary gland[7] or the adrenal cortex.[8,9] The role of these two organs thus has assumed great importance.

The next development, however, again pointed to the pancreas. It was found[10] that when one produces diabetes by the injection of anterior pituitary extracts, the ultimate damage is to the pancreas, and the islets of Langerhans undergo characteristic changes (first over-stimulation of the beta cells, later hydropic degeneration, degranulation, hyaline degeneration, and eventually fibrosis). The same is true to a lesser extent with the adrenal cortex so that despite the importance of the pituitary and the adrenal the pancreas must still be considered as a highly important organ in the pathogenesis of diabetes.

It was found in 1943 by Dunn, Sheehan, and McLetchie[11] that the injection of alloxan into animals caused destruction of the islands of Langerhans of the pancreas. Immediately the question arose, "Is it possible that alloxan has something to do with human diabetes?" People set to work at once to find out whether there was enough alloxan in the body to be implicated. Not enough was found, so that the idea was abandoned for the moment. A couple of years later it was discovered that alloxan when injected into animals causes a definite reduction in the content of glutathione in the blood.[12] With this clue Dr. Lazarow[13] of Cleveland was the first to prove that if one injected glutathione before giving alloxan, one could prevent the diabetogenic action of the alloxan compound. Dr. Lazarow and others have expanded this further to show that other sulfhydryl-containing compounds injected into animals before alloxan would prevent the action of alloxan in producing diabetes.

Just this past year, Griffiths[14] of Australia, putting together the facts that

alloxan is closely related to uric acid and that sulfhydryl compounds including glutathione protect against the diabetogenic action of alloxan, reasoned that if the glutathione content of the blood were lowered the way might be opened for uric acid to act in the same way as alloxan in producing diabetes. Accordingly he placed rabbits on a methionine-cystine-free diet which did result in a lowering of the blood glutathione. He then gave them uric acid intraperitoneally and succeeded in producing a transient but well-defined hyperglycemia and glycosuria lasting several days. The blood sugars ranged from 200 to 250 mg. per cent. The injection of uric acid produced the same type of blood sugar curve in the first few hours following the injection as did the administration of alloxan. Both substances give rise to a tri-phasic curve, an original hyperglycemia followed by a hypoglycemic phase, and then in a few hours a permanent—more or less permanent in the case of uric acid—hyperglycemic level. This common property of the two chemically related substances is suggestive. It is important that in Griffiths' experiments the animals in which the glutathione levels of the blood were not lowered by this previous diet did not show glycosuria or hyperglycemia.

The next step and, so far as I know, the last step, was taken by Dr. Conn and co-workers[15] of Ann Arbor during the past year. Dr. Conn gave a purified preparation of adrenocorticotropic hormone of the pituitary to normal human beings and produced definite glycosuria and hyperglycemia, accompanied by a fall of blood glutathione and a considerably increased excretion of uric acid in the urine. It thus appears that the activity of the "pituitary-adrenal axis" in producing diabetes may involve, at least in part, the same mechanisms that are involved in alloxan diabetes.

One must proceed from here on grounds of speculation only. It is possible that glutathione, being protective against alloxan, is protective also against uric acid; that if one lowers the glutathione content of the blood or tissues and then presents the organism with any diabetogenic agent—an agent which will put a strain on the islet mechanism—the islets being no longer protected by an adequate amount of glutathione will then succumb and the diabetic state will supervene.

Certainly uric acid has not been demonstrated to be the cause of human diabetes. However these recent findings do open certain cracks in the wall of ignorance which has confronted us.

Another recent development has been in connection with the matter of insulin resistance, or perhaps a better term would be anti-insulin substances. It has been known for a long time that in the anterior pituitary and the adrenal cortex there do exist diabetogenic substances which may also be anti-insulin in action. This is also true of the thyroid to a somewhat lesser degree. Recently facts have been accumulating which suggest that there may be an anti-insulin substance in the pancreas itself. This would indeed be a paradox, to have the organ which produces insulin also prove to contain an anti-insulin substance as well. It is not an unprecedented situation but it is striking if true.

What are the facts to suggest that possibly the pancreas may possess an anti-insulin factor? First, in totally depancreatized dogs, as found by Drag-

stedt[16] some years ago, the requirement for insulin is less than it is in partially depancreatized dogs on the same diet. Second, the pituitary diabetic dogs of Young,[17] (the investigator who originally produced permanent diabetes by pituitary injections), required less insulin after pancreatectomy than they did when they were diabetic merely from a pituitary point of view. It should not be forgotten that the pituitary injections they had received had damaged the islet cells and that they were in the last analysis pancreatic diabetic dogs too. But the fact was that when the pancreas was removed, they needed less insulin than when the pancreas was in.

Third, if the dog made diabetic with alloxan has his insulin requirement carefully determined and is then subjected to pancreatectomy, his requirement for insulin is less after total removal of the pancreas than it was in the alloxan diabetic state.[18] Fourth, recent developments in surgery have permitted the complete removal of the pancreas in man for cancer or sclerosis of the pancreas. The remarkable thing about these patients is that with no pancreas at all, none of them has required more than 40 units of insulin a day.[19] If one contrasts this with the insulin requirement of many spontaneously diabetic patients who need 60, 80 or 100 units a day, it becomes apparent at once that in these spontaneously diabetic patients, there must be something other than a pure insulin deficiency at work.

Finally, it has been known for some time that the intravenous injection of purified preparations of insulin—at least the preparations made in this country—is followed by a transient hyperglycemic phase before the hypoglycemia supervenes. This suggested the possibility that somehow in the preparation of insulin a substance antagonistic to it also was incorporated. The latest development in this field was the announcement from McGill University during the past year to the effect that if the supernatent fluid from the first isoelectric precipitate of insulin is subjected to certain further treatment and injected into rats, the liver glycogen of the rats is reduced to one-third the normal and the blood sugar is nearly doubled.[20] It was found that there was no adrenalin present in these extracts and there was no histamine. Extracts of other organs in the hands of these investigators had no such effect. This work has recently been confirmed by Sutherland and de Duve.[21] (However, they found some similar effect from cells of the gastrointestinal mucosa.) This phenomenon was ascribed by the Montreal workers to an alpha cell hormone. For years we have been wondering what the alpha cells were doing there. Nobody could prove that they did anything. The possibility existed, of course, that they had a hormonal function of some sort. Whether the insulin antagonizing action of these extracts is actually due to an alpha cell hormone it is too early to say with finality.

Another recent development has come from the use of isotopes in the study of glycogen and fat metabolism and the function of insulin. The studies I should like to tell you about have emanated largely from the laboratory of Dr. DeWitt Stetten.[22] Dr. Stetten fed normal rats a diet containing 15 Gm. of carbohydrate per day, and labeled this carbohydrate with deuterium—heavy water. By so doing he was able to analyze various parts of the animals and

determine how much glycogen there was in each part and whether that glycogen had come from the diet or from some other source. The astonishing thing about this investigation was that from this 15 Gm. of carbohydrate in the diet per day, the rats deposited only 0.44 Gm. of liver glycogen per day. This represents only 3 per cent of their dietary intake of carbohydrate and this amount of glycogen is sufficient to supply the animal with energy needs for only thirty minutes. This casts a new light on the relative importance of glycogen in the animal economy. Dr. Stetten also was able by means of this isotopic technic to find out how much of the dietary carbohydrate was converted to fat. He found that 2 Gm. of fat were deposited per day in contrast to the 0.44 Gm. of glycogen. Thus, these normal rats made roughly five times as much fat as they did glycogen from the dietary carbohydrate, and to do this it required ten times as much carbohydrate.

What happened in the diabetic rat? The diabetic rat, instead of manufacturing 2 Gm. of fat per day from this diet, manufactured only 0.1 Gm. from these dietary sources or only 5 per cent of the normal. Thus, the absence of insulin prevented the animal from laying down or synthesizing fat at anywhere near a normal rate. This is one of the newer concepts of the function of insulin. It has yet to be elaborated but again is a highly interesting lead, and likely to revise our concepts of what insulin does and of the relative importance of fat and carbohydrate in the diabetic organism.

One of the things which we have learned in the past few years is that we must give more insulin sooner in diabetic coma. Rather than too little and too late, we had better give too much too soon. One can make up for giving too much insulin—one cannot make up for giving too little because the patient may pass beyond the stage in which insulin will be of any avail. Generally speaking, there is a rough correlation between the height of the original blood sugar in acidosis and the amount of insulin required to bring the patient out of coma. It is highly important that anyone dealing with diabetic coma have access to a laboratory in which determinations of blood sugar and carbon dioxide combining power can be performed. Many things happen to patients during coma which are not reflected promptly enough by the urinalyses. Hence the importance of a laboratory that will do the more complicated procedures cannot be overemphasized.

I think that the original dose of insulin in diabetic coma should never be less than 100 units in an adult patient. Within the first three hours the patient should receive from two to three times the original dose. How much should be given afterwards depends on circumstances so that it is difficult to lay down any general rules. The point I should like to stress is that instead of beginning with 40 units or 60 units or 80, one should begin with 100 in most cases. One need not be afraid of hypoglycemia; it may occur, but it can be corrected.

The second development in the field of diabetic acidosis has been the increasing recognition of the importance of electrolytes other than sodium. Potassium, phosphorus, and magnesium have been found to be depleted in many patients with diabetic acidosis. Many patients have been lost in coma

because of failure to recognize that these elements of blood are almost as important as those we have been used to thinking of. In 1946 Holler[23] published his brilliant observation concerning a patient with diabetic acidosis who had been successfully treated at first but a few hours afterward took a turn for the worse. The respirations became labored, muscular weakness became extreme, and Holler had the wit to recognize that this was one of the manifestations of potassium deficiency. The patient was treated with potassium chloride and recovered. Since that time, a good many cases have been reported, some with chemically proved hypokaliemia, others with conjectured hypokaliemia. Martin and Wertman[24] published in 1947 statistics on a number of cases of coma in 46 per cent of which there was a low potassium which developed during treatment. The potassium was not low in the beginning but developed as treatment progressed; the lowest value they found was 1.9 milliequivalents per liter.

Thirty-six per cent of these patients also had a chemically determined magnesium deficiency. The symptoms of potassium lack are muscular weakness, and respiratory difficulty which is in essence a respiratory paresis or paralysis and is different from the Kussmaul type of breathing. It is an effortful respiration with the accessory muscles being used freely. Finally, changes in the electrocardiogram are observed consisting specifically of a lowering of the T waves in patients whose potassium is considerably below normal. There are, of course, apt to be other abnormalities in severe diabetic coma including depression of the ST segment and prolongation of the QT. These are not specific for low potassium, may occur as a result of coma itself, may of course represent coronary disease, and must be interpreted with some caution in respect to the problem of potassium. The lowering or inversion of the T waves, if one can exclude coronary disease, is highly suggestive in the presence of the other symptoms mentioned.

The decline in potassium is probably caused by several factors. One is the depletion of serum potassium as well as other electrolytes by the profuse diuresis which patients in acidosis customarily exhibit. If one gives intravenous glucose, one serves only to accentuate this diuresis, another reason in my opinion why intravenous glucose should not be used in the treatment of diabetic coma. Second, the administration of large amounts of fluids dilutes the electrolytes. Third, there is the specific effect of insulin. Insulin injected into any organism in sufficient amounts causes lowering of the serum potassium; the large amounts which are employed in diabetic coma must necessarily have a considerable effect in this direction.

The drop in potassium does not occur early. The potassium level on the admission of the patient is usually normal or high, and it declines only some hours after treatment is begun. Should potassium be given routinely in the treatment of diabetic coma? I think not. Not more than one-half of these patients show any potassium depletion, and only a fraction of them have values low enough to be of serious significance. One has to watch for the development of suggestive symptoms, and measure potassium levels if possible. One must be exceedingly careful, however, about giving any potassium to

patients showing impaired renal function. The dose of potassium which can be given has been stated by some to be 0.6 Gm. by mouth every half hour for 6 doses, or intravenously 1.5 Gm. of potassium chloride as a 2 per cent solution. This is potentially a hazardous procedure since large amounts of potassium given to a normal person may produce damage. As a matter of fact, 2 Gm. by mouth have been shown to produce definite changes in the electrocardiogram.

Like potassium, phosphorus has been shown to decline during the treatment of diabetic coma. Whether it is as important as potassium is at this moment open to question. But certainly the phosphorus levels do decline and for much the same reasons as do the potassium levels. Franks, Berris, Kaplan, and Myers[25] demonstrated that the administration of 1.319 to 2.638 Gm. of phosphorus as sodium phosphate to patients in diabetic acidosis led to the retention of 85 to 90 per cent of the amount injected, and even this was not sufficient fully to correct the rather high degree of phosphorus depletion.

In 1900, diabetic coma caused 64 per cent of the deaths from diabetes; cardiovascular renal disease caused 18 per cent. Today diabetic coma causes death in only 3 per cent of those who die with diabetes and cardiovascular renal disease is involved in 67 per cent as the prime cause of death. The percentages are thus almost completely reversed.

In Joslin's [26] clinical experience from 1944 to 1946 there were 651 deaths with diabetes. Sixty-seven per cent of these were due to arteriosclerosis; 44.5 per cent of the total deaths were caused by arteriosclerotic lesions of the heart.

From the autopsy reports of Warren[27] we have a similar picture. Among 484 autopsies on patients dying with diabetes 30 per cent of the deaths were caused by arteriosclerosis, and of this group 57 per cent were due to cardiac causes. In 61 autopsies on patients with diabetes of fifteen years' duration or over—this is an important point—57 per cent died of arteriosclerotic lesions.

In 1947 Dolger[28] published a discouraging report. He found that of 200 regularly examined patients with diabetes up to 25 years' duration, none had escaped retinal hemorrhage regardless of age of onset, severity of the disease or method of treatment. Fifty per cent had hypertension and albuminuria at the time the first retinal hemorrhage was discovered, and in 14 per cent the patients lost their vision completely.

Equally distressing were the figures of White and Waskow[29] which appeared a little later. They had studied 200 diabetics with the onset of disease in childhood who had survived for twenty years. The incidence of vascular lesions in this group was 92 per cent. Cerebral vascular accidents had occurred in 2.5 per cent, coronary insufficiency in 8 per cent, albuminuria in 30 per cent, hypertension in 30 per cent, nephritis in 50 per cent, calcified arteries by x-ray in 75 per cent, retinal hemorrhages in 80 per cent, and sclerosis of the retinal vessels in 85 per cent. The frequency of these complications in the younger diabetics is of increasing concern to all physicians.

What causes these lesions of the arteries, the veins and the capillaries? Is it hyperglycemia, is it hyperlipemia, or is there possibly some third factor, a factor perhaps which gives rise at the same time to the tendency to have

diabetes on the one hand and the tendency of the blood vessels to be affected on the other? The answers to these questions are not at hand. Experimentally hyperglycemia has never been proved to produce vascular lesions. But one should bear in mind that so far as this point is concerned, there are probably not more than a half dozen diabetic animals in the recorded literature which have been carefully observed for long enough to determine this matter conclusively. The administration of cholesterol is well known to cause atherosclerosis in animals but has never been shown to cause retinal hemorrhages. Certainly retinal hemorrhages are part and parcel of the general vascular disease and until retinal hemorrhages as well as atherosclerosis of the larger vessels can be produced by experimental means one cannot be said to have reproduced the total vascular picture of diabetes.

In human beings the data are not conclusive. The statement is often made that degenerative complications occur regardless of the degree of control of glycosuria. That statement is, I think, difficult to support. The vast majority of juvenile diabetics—but not quite all—have not been and cannot be well controlled with our present methods. Thus the allegation that diabetics regardless of the degree of control have such complications seems to me to be rather meaningless. I think most younger diabetic patients have not been rigorously controlled over a period of many years. There is one group which is an exception, the patients of Boyd, Jackson and Allen[30] at the University of Iowa. These workers believe thoroughly in keeping the urine sugar free at all times if possible. They have taken full advantage of their unusual opportunities to follow their young diabetic patients carefully for long periods. They recently reported a study of 69 patients whose disease had begun in childhood and who returned for follow-up examinations after periods of five to ten years. Of the 69, 17 were of sub-standard height at the first examination and 13 of them resumed normal rate of growth under the strict regimen of a sugar-free urine and a normal blood sugar. There were 12 dwarfs at the terminal examination, none of them having well controlled diabetes. There were 11 with retarded maturation, none of them having been well controlled children. There were 6 examples of enlargement of the liver all of which subsided with the strict regimen Dr. Boyd employs. There were 6 examples of retinal hemorrhage all of them being related to periods of poor control. There were 6 cases with clinically demonstrable cataracts again all occurring in poorly controlled cases. About 20 patients had minor lenticular opacities none of them occurring in well controlled patients.

Thus, while the satisfactory control of the young diabetic patient is a difficult feat and is often impossible, it can be done under exceptional circumstances and when it is the results, with respect to the prevention of degenerative complications, are worth it.

References

1. Blotner, H. and Hyde, R. W.: Studies in diabetes mellitus and transient glycosuria in selectees and volunteers. New England J. Med. **229**:885-892 (Dec. 9) 1943.
2. Blotner, H.: Studies in glycosuria and diabetes mellitus in selectees. J.A.M.A. **131**:1109-1114 (Aug. 3) 1946.
3. Wilkerson, H. L. C., and Krall, L. P.: Diabetes in a New England town. J.A.M.A. **135**:209-216 (Sept. 27) 1947.

4. Young, F. G.: Permanent experimental diabetes produced by pituitary (anterior lobe) injections. Lancet **2**:372-374 (Aug. 14) 1937.
5. Ingle, D. J.: Production of glycosuria in normal rat by means of 17-hydroxy-11-dehydrocorticosterone. Endocrinology **29**:649-652 (Oct.) 1941.
6. Ingle, D. J., Sheppard R., Evans, J. S., and Kuizenga, M. H.: Comparison of adrenal steroid diabetes and pancreatic diabetes in rat. Endocrinology **37**:341-356 (Nov.) 1945.
7. Houssay, B. A., and Biasotti, A.: Le diabète pancréatique des chiens hypohysectomisés. Compt. rend. Soc. de Biol. **105**:121-123 (Oct. 16) 1930.
8. Hartmann, F. A. and Brownell, K. A.: Relation of adrenals to diabetes. Proc. Soc. Exper. Biol. and Med. **31**:834-835 (April) 1934.
9. Long, C. N. H. and Lukens, F. D. W.: Observations on adrenalectomized, depancreatized cats. Science **79**:569-571 (June 22) 1934.
10. Richardson, K. C. and Young, F. G.: Histology of diabetes induced in dogs by injection of anterior-pituitary extracts. Lancet **1**:1098-1101 (May 14) 1938.
11. Dunn, J. S., Sheehan, H. L. and McLetchie, N. G. B.: Necrosis of islets of Langerhans produced experimentally. Lancet **1**:484-487 (April 17) 1943.
12. Leech, R. S. and Bailey, C. C.: Blood alloxan and blood glutathione in rabbits injected with alloxan. J. Biol. Chem. **157**:525-542 (Feb.) 1945.
13. Lazarow, A.: Protective effect of glutathione and cysteine against alloxan diabetes in the rat. Proc. Soc. Exper. Biol. and Med. **61**:441-447 (April) 1946.
14. Griffiths, M.: Uric acid diabetes. J. Biol. Chem. **172**:853-854 (Feb.) 1948.
15. Conn, J. W., Louis, L. H., and Wheeler, C. E.: Production of temporary diabetes mellitus in man with pituitary adrenocorticotropic hormone: relations to uric acid metabolism. J. Lab. and Clin. Med. **33**:651-661 (June) 1948.
16. Dragstedt, L. R., Allen, J. G., and Smith, E. M.: Extensive insulin tolerance in diabetic dogs. Proc. Soc. Exper. Biol. and Med. **54**:292-294 (Dec.) 1943.
17. Young, F. G.: Anterior pituitary gland and diabetes mellitus. New England J. Med. **221**:635-646 (Oct. 26) 1939.
18. Thorogood, E. and Zimmerman, B.: Effects of pancreatectomy on glycosuria and ketosis in dogs made diabetic by alloxan. Endocrinology **37**:191-200 (Sept.) 1945.
19. Ricketts, H. T., Brunschwig, A., and Knowlton, K.: Effects of total pancreatectomy in a patient with diabetes. Am. J. Med. **1**:229-245 (Sept.) 1946.
20. Heard, R. D. H., Lozinski, E., Stewart, L. and Stewart, R. D.: Alpha-cell hormone of the islets of Langerhans. J. Biol. Chem. **172**:857-858 (Jan. 12) 1948.
21. Sutherland, E. W. and deDuve, C.: Origin and distribution of hyperglycemic-glycogenolytic factor of pancreas. J. Biol. Chem. **175**:663-674 (Sept.) 1948.
22. Stetten, DeW., Jr.: Altered rates of certain metabolic processes in hypo- and hyperinsulinism. Proc. Am. Diab. A. **7**:69, 1947.
23. Holler, J. W.: Potassium deficiency occurring during treatment of diabetic acidosis J.A.M.A. **131**:1186-1189 (Aug. 10) 1946.
24. Martin, H. E. and Wertman, M.: Serum potassium, magnesium and calcium levels in diabetic acidosis. J. Clin. Investigation **26**:217-228 (March) 1947.
25. Franks, M., Berris, R. F., Kaplan, N. D., and Myers, G.: Metabolic studies in diabetic acidosis. Arch. Int. Med. **81**:42-55 (Jan.) 1948.
26. Joslin, E. P. et al: The Treatment of Diabetes Mellitus, ed. 8. (Philadelphia: Lea and Febiger, 1946) p. 229.
27. Warren, S.: The Pathology of Diabetes Mellitus, ed. 2. (Philadelphia: Lea and Febiger, 1938).
28. Dolger, H.: Clinical evaluation of vascular damage in diabetes mellitus. J.A.M.A. **134**:1289-1291 (Aug. 16) 1947.
29. White, P. and Waskow, E.: Clinical pathology of diabetes in young patients. South. M. J. **41**:561-567 (June) 1948.
30. Boyd, J. D., Jackson, R. L. and Allen, J. H.: Avoidance of degenerative lesions in diabetes mellitus. J.A.M.A. **118**:694-696 (Feb. 28) 1942.

TRANSORBITAL INTRACRANIAL STAB WOUNDS

C. C. McCLURE, Jr., M.D. and W. JAMES GARDNER, M.D.

Department of Neurosurgery

FOUR cases of transorbital intracranial stab wounds are presented, each one illustrating a different clinical picture and demonstrating the vulnerability of the brain when approached through the thin-walled, funnel-shaped orbit.

Although much has been written concerning the incidence of wounds of the cranial contents as well as numerous articles pertaining to wounds of the orbital contents, relatively little has appeared about wounds which involve the intracranial structures by way of the orbits. This is difficult to understand since this is one of the most accessible modes of entry to the brain for stabbing instruments. Possibly it is due to the fact that most such serious wounds are rapidly fatal while some of the milder cases are undiagnosed because they exhibit few intracranial symptoms. These 4 cases serve to illustrate several of the possibilities which may be encountered in such wounds.

A group of war wounds involving the orbit and adjacent brain structures is discussed by Webster, Schneider and Lofstron.[1] These were often injuries caused by high explosives and significant in the damage produced. The mortality in their series was 12.5 per cent as compared with a mortality rate of 6.4 per cent in penetrating wounds of the cranium generally. According to Courville and Schillinger,[2] Kuntzman reports the case of a patient who stuck a pencil through the roof of the orbit into the brain, developed meningitis and died. Evatt[3] reports a case of an ice pick stab in the orbit which was first seen three hours after admission and which was so firmly embedded that it required the efforts of two men to pull it from the wound. This patient suffered no impairment of the eyesight.

Anatomical Considerations

The orbit is a pyramidal, cone or funnel-shaped cavity which is formed by various bones of the cranium and face. It contains the eyeball and structures relating thereto. The eyeball itself is a tough, elastic globe which is readily movable in its bed of fat making it less liable to injury from penetrating wounds. The superior wall of the orbit is formed by the frontal and sphenoid bones. The medial wall is made up of the lacrimal, ethmoid and sphenoid bones and the lateral wall is made up of the zygomatic, sphenoid and frontal bones. There are several openings in the orbit. The largest is the aditus which is the opening to the exterior. The optic foramen, which transmits the optic nerve and the ophthalmic artery, is situated at the back of the orbit. The sphenoidal fissure is located on the superolateral surface of the orbit and transmits the third, fourth, the ophthalmic division of the fifth and the sixth nerves; also

some filaments from the cavernous plexus of the sympathetic and the orbital branches of the middle meningeal artery. Passing out through the fissure are the ophthalmic vein and the recurrent branch from the lacrimal artery to the dura. On the inferolateral surface is the inferior orbital fissure which transmits the maxillary nerve and its zygomatic branch, the infra-orbital vessels and the ascending branches from the sphenopalatine ganglion. In the fronto-ethmoidal suture are the anterior and the posterior ethmoidal nerve and the ethmoidal vessel. These comprise the more important of the openings of the orbit. Thus, the orbit is a funnel-shaped cavity which would tend to deflect penetrations posteriorly through one of the numerous openings and thence into the brain which lies above and behind it. Freeman[4] has pointed out the ease with which the roof of the orbit may be penetrated to reach the frontal lobes of the brain in the performance of a transorbital prefrontal leucotomy.

High speed projectiles entering the orbit are apt to lacerate or rupture the eyeball. Conversely, a slower moving stabbing instrument is not so likely to damage the globe because the blinking reflex covers the eyeball with tough skin which, in effect, blunts the stabbing instrument. At the same time, the slower velocity of the stabbing instrument enables it to overcome the inertia of the tough globe which is shoved to one side in its puddle of fat.*

**This is analagous to the stab wounds of the peritoneal cavity. Such wounds tend to push aside the intestines rather than to penetrate them, as is seen in gunshot wounds.*

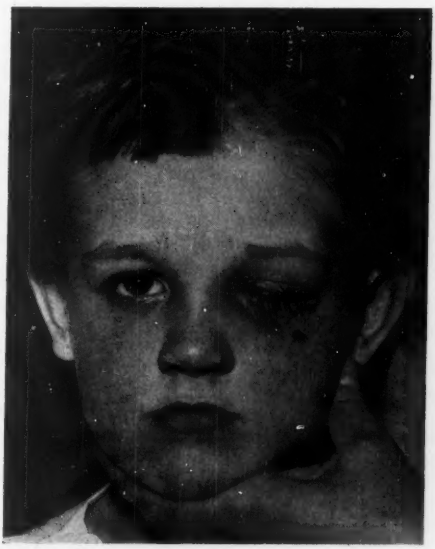


Fig. 1. Case 1. Four days after injury.

Case Reports

Case 1. A four-year-old boy was admitted to the Cleveland Clinic Hospital. At ten o'clock on the morning of admission, the patient had fallen on a pitch-fork blade which was driven through the inner part of his left upper eyelid. He was taken to his local doctor who sent him to an eye specialist. Here it was found that there was leakage of spinal fluid from the wound. He was given 100,000 units of penicillin intramuscularly, and sent into the hospital by ambulance. By the time he arrived, he had vomited two or three times, and was complaining of pain in the back of his neck. There had been no other symptoms.

Physical examination showed the temperature to be 98.6 F. and the pulse 116. He did not appear acutely ill. Examination of the eyes showed that the left eyelid was blue and swollen completely closed. There was an irregular wound ½ inch in length on the inner aspect of the upper lid which was draining slightly blood-tinged cerebrospinal fluid. When the eyelids were forced apart the globe appeared normal. Examination of the cranial nerves revealed them to be intact. The reflexes were all normal and there were no pathologic reflexes. There were no motor or sensory paralyses.

X-rays showed a variation of the appearance of the superior orbital wall on the left side; this wall appeared thickened and there was a questionable translucent line extending through the superior orbital wall. The impression was "Localized changes involving superior orbital wall on left—old trauma?"

The diagnosis at the time of admission was "Penetrating wound, brain, transorbital route with cerebrospinal fluid leak." The patient was placed on penicillin, 30,000 units every three hours for five days and was given a dose of tetanus and gas gangrene antitoxin.

The leakage of cerebrospinal fluid stopped two days after admission. The edema of the lid gradually diminished during the hospital stay and at the time of the patient's discharge on the eighth hospital day, the eye was open, the pupillary and extraocular movements were normal and there was no evidence of injury to the globe.

Because of the absence of cerebral symptoms in this case, the intracranial wound might

Fig. 2. Case 2. Eleven days after injury.

FIG. 3. Case 3. Twenty-one days after injury.

not have been suspected if there had not been leakage of the cerebral fluid from the wound (fig. 1).

Case 2. An 18-year-old boy was observed with a chief complaint of being unable to open the left eye. Nine days before, while playing football in a stubble field, he was tackled and thrown face down. He immediately experienced an excruciating flash of pain about the left eye and the forehead and on arising was unable to open his left eye. He was told that he had a "scratch" on the left lower eyelid.

On examination, the patient exhibited a complete paralysis of the left third, fourth and sixth cranial nerves and the ophthalmic division of the fifth. There was a small, partially healed laceration on the lower lid. There was no tenderness, ecchymosis, audible bruit or pulsation. Vision in the eye was good and funduscopic examination was satisfactory. X-rays of the skull and orbits were reported as normal.

Diagnosis at that time was "Stab wound of left orbit through the sphenoidal fissure resulting in interruption of the cranial nerves transmitted through the latter."

Three days later, the laceration on the lower lid became swollen. The margins of the wound were separated and, with a hemostat, two pieces of grass stubble were removed from deep within the orbit. The wound was treated with sulfa powder locally and diathermia to the orbit, and rapidly healed. The neurologic aspects slowly improved, and the patient was discharged on the ninth hospital day. When last seen, he had partial return of eye motion and could open the eye.

In this case we have an example of a wound which might well have injured the eyeball but, instead, pushed it aside and it escaped injury. This case also serves to illustrate that even an insignificant external wound may be the cause of a complete and possibly permanent external ophthalmoplegia (fig. 2).

Case 3. A 37-year-old man entered the Cleveland Clinic Hospital with a history of having been struck with a large wooden splinter which had entered the right upper eyelid, and the orbital cavity into the brain. This had occurred twelve days prior to admission, The patient had been sawing lumber into strips with a rotary saw when a broken piece.

thrown forcibly, struck him with the irregular end. The splinter, three feet long, was removed by fellow workmen before admission to his local hospital. When first seen by his local doctor, profound shock was present with loss of consciousness and bleeding from the nose. The patient was put to bed and treated for shock. Intravenous fluids were administered, and the patient vomited some "coffee grounds" material. After about twelve hours the patient recovered from shock and was able to talk coherently in about twenty-four hours. It was then noticed that he had a paralysis of the left arm and leg and there was incontinence of urine and feces. The right eyeball appeared intact, but there was no vision in the right eye.

Physical examination on admission to the Cleveland Clinic Hospital showed a temperature of 99.6 F., pulse rate of 46, and blood pressure of 100/80. The patient brought with him the stick which was three feet long and roughly a half an inch in diameter. The jagged end was bloody for three inches indicating that this portion had penetrated. There was a granulating wound of the right eyelid above the inner canthus with ptosis of this lid. The right pupil was dilated and did not react to light or accommodation. There was no light perception, and no extraocular movements in this eye. Funduscopic examination was negative except for some retinal edema. The patient had spells of involuntary crying. There was complete, flaccid left hemiplegia. The deep reflexes were normal, but the abdominal reflexes on the left were absent. The Babinski was negative but there was a positive Kernig's sign.

Lumbar puncture on admission disclosed a pressure of 190 mm. with normal dynamics. The fluid was clear but a deep orange in color. It showed a trace of globulin and the total protein was 50 mg. The cell count was 1. Spinal fluid culture was satisfactory as was the urine. Examination of the blood showed a hemoglobin of 14.5 Gm. and a white blood cell count of 11,350. X-rays showed a normal skull and normal orbits with no evidence of foreign bodies.

The diagnosis was "Penetrating wound of the brain through the right orbit with internal and external ophthalmoplegia."

Because of the possibility that hemiplegia might be due to laceration of the right internal carotid artery rather than the brain wound, a right carotid arteriogram was made. There was no visualization of the right anterior cerebral artery.

The patient was given 50,000 units of penicillin every three hours for ten days and became afebrile in twenty-four hours. He was discharged after eleven days in the hospital. with the paralysis still present. About one week after discharge his right eye began to open and he became able to walk with a cane. In about three months he could move the eye in all directions but there was no return of vision and only slight return of motion in the arm.

This illustrates a case of a violent wound of the orbit which penetrated the brain to a depth sufficient to produce hemiplegia in addition to the local ocular paralysis but in which the eyeball was not damaged (fig. 3).

Case 4. A colored man, 22 years of age, was picked up by police from the gutter outside a tavern. He was taken to a hospital where he was seen to be literally covered with blood. He could at no time give an account of events leading up to injury.

On entry, physical examination revealed a patient in coma, with Cheyne-Stokes respiration. The blood pressure was 120/80. There was severe rigidity of the neck. The right pupil was fixed and did not react to light. There were no hemorrhages in either fundus. There was swelling of the left eyelid. There was a stab wound on the left side of the neck which was probed and found to be .5 cm. deep. There was no hematoma. Convulsive-like movements were noted involving the right arm. The left arm was motionless although the other extremities thrashed about. The deep reflexes were found to be somewhat hypoactive but were bilaterally equal. There was a positive Babinski on the right.

A lumbar puncture upon admission showed bloody spinal fluid, but this was thought to be due to trauma of the puncture. A diagnosis of stab wound of the neck and cerebral contusion with acute alcoholism was made. He rapidly developed swelling of the contents o both orbits. By the third hospital day, he became rational and neurologic findings cleared. The blood count at this time revealed 58 per cent hemoglobin, 2,830,000 red blood cells, and 6.400 white blood cells. The urine was negative. The temperature ranged from 99 to 102 F. throughout the course of the illness. On the ninth hospital day, he had a severe

FIG. 4. Case 4. Twelve days after injury. (Nasal packs were inserted to control nasal hemorrhage.)

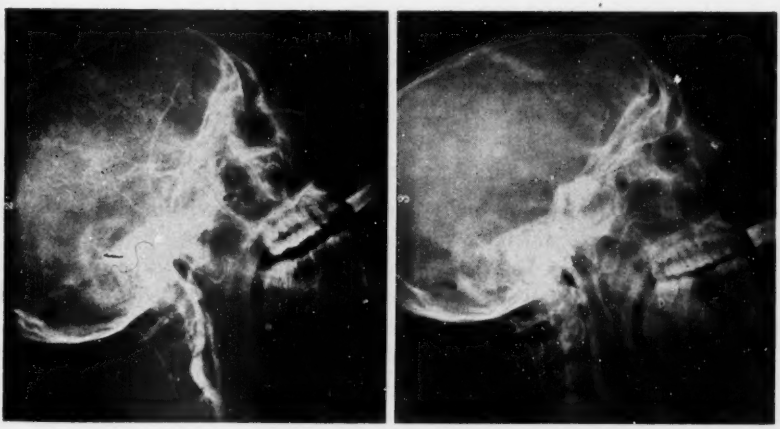


FIG. 5. (a) Case 4. Left carotid arteriogram, showing normal filling of arterial system. (b) Case 4. Right carotid arteriogram, showing carotid-cavernous sinus arteriovenous fistula.

hemorrhage from the nose and almost bled to death. It was finally controlled with postnasal packs. About the same time he lost all light perception in both eyes. Three days later, he had a recurrence of the nasal hemorrhage. On the fourteenth hospital day, a neurosurgical consultation was obtained. At this time the patient's orbital contents were in a state of extreme protrusion due presumably to posterior orbital hematomas (fig. 4). A small wound of the left lower eyelid was found at this time. This finding together with the clinical course led the examiner to suspect that the patient had sustained a stab wound through the left orbit into the base of the skull with laceration of one of the internal carotid arteries, probably the right, in view of the dilated, fixed right pupil and paresis of the left arm. Carotid arteriograms were advised. The patient received a blood transfusion and on the sixteenth day arteriograms were made. The left arteriogram was performed first and showed normal findings so the right arteriogram was made. This disclosed the typical picture of a carotid cavernous arteriovenous fistula (fig. 5a and 5b). During the procedure, the patient's respiration ceased, but by the use of stimulants and artificial respiration, it was again established. Ligatures were applied to the right external, internal and carotid arteries and the latter vessel was divided between the ligatures. The patient's condition did not permit intracranial ligation.

The patient failed to rally following the procedure and died forty-eight hours later. Postmortem examination was performed by the coroner and disclosed a laceration of the right carotid artery and cavernous sinus. There was an old hematoma at the base of the right temporal lobe. There was also a subdural hematoma on the convex side of both hemispheres and hematomas of both orbits. The diagnosis was not suspected for two weeks because attention had been directed to the neck while the actual wound of entry was overlooked.

Case 4 serves to illustrate that no matter how trivial a wound may be, its possibilities should be thoroughly explored in the light of developing symptoms even if they implicate the opposite side of the brain. Also, in arteriovenous fistulae involving the internal carotid artery and the cavernous sinus, the carotid artery should be ligated above the cavernous sinus before ligating it in the neck. This has been emphasized by Sweet and Bennett[5] who found that in carotid cavernous sinus arteriovenous fistulae, the affected carotid maintains an intravascular pressure which, in effect, plugs up the defect there by allowing blood from the opposite carotid to circulate through both sides of the brain. When the affected carotid is ligated in the neck this cuts off the counter pressure and allows blood from the unaffected carotid to pass from the homolateral hemisphere out through the defect thus depriving the brain circulation of a corresponding amount of blood.

Summary and Conclusions

1. Four cases of transorbital stab wounds are presented each of which serves to illustrate a different type of intracranial damage.

2. In stab wounds of the orbit, the eyeball frequently escapes injury.

3. The possibility of an intracranial wound should be considered in all cases of stab wounds of the eyelids.

4. In cases of carotid cavernous sinus fistulae, the carotid artery should be ligated intracranially before ligation in the neck.

References

1. Webster, J. E., Schneider, R. C., and Lofstrom, J. E.: Observation upon management of orbito-cranial wounds. J. Neurosurg. 3:329-336 (July) 1946.

2. Courville, C. B., and Schillinger, R. J.: Intracranial complication of disease of eye and orbit. Bull. Los Angeles Neurological Soc. 11:120-110 (Sept.) 1946.
3. Evatt, C. W.: Ice-pick through orbit; case report. J. South Carolina M. A. 43:236 (Aug.) 1947.
4. Freeman, W.: Transorbital leucotomy. Lancet, p. 371 (Sept. 4) 1948.
5. Sweet, W. H., and Bennett, H. S.: Changes in internal carotid pressure during carotid and jugular occlusion and clinical significance. J. Neurosurg. 5:178-195 (March) 1948.

MEDICAL TREATMENT OF ACUTE TOXIC ULCERATIVE COLITIS

Report of Two Cases

CHARLES H. BROWN, M.D., and JOSEPH H. PERRY, III, M.D.
Department of Gastroenterology

THE treatment of the desperately ill toxic patient with fulminating ulcerative colitis is a medical problem that challenges the ingenuity and knowledge of the practitioner. Not infrequently the patience of the physician is exhausted and he recommends an ileostomy as a "life-saving measure." Bargen,[1] however, has repeatedly stressed the fact that the surgical mortality in these patients is high, while the medical mortality is relatively low. They are poorly nourished, febrile, in negative nitrogen balance, and are poor surgical risks. Consequently, it would seem that intensive medical treatment would have more to offer these patients than surgery.

At the Cleveland Clinic, surgery is reserved largely for those patients with ulcerative colitis who present complications of the disease. Approximately 13 per cent are operated on here, as compared with 26 per cent at the Lahey Clinic,[2] and 5.5 per cent at the Mayo Clinic.[1]

There is no specific medical treatment for the acutely ill, toxic patient with ulcerative colitis. The principal purpose of treatment is to improve his nutrition and to decrease the inflammation of the colon. The treatment of each patient is different and must be individualized. The results are frequently gratifying with the toxicity of the patient and the inflammation of the colon subsiding, and the nutrition improving. Frequently, the acutely ill, toxic patient improves remarkably and is left with little or no residual.

Recently we had the opportunity of treating 2 patients acutely ill with ulcerative colitis with gratifying results. Several relatively new therapeutic aids employed were apparently beneficial. Because similar treatment may be helpful to other patients seriously ill with the same disease, we present 2 cases.

Case Reports

Case 1. A twelve-year-old boy was admitted to the Cleveland Clinic Hospital on December 26, 1948. He gave a history of having developed lower abdominal colicy pain, diarrhea with purulent serosanguineous stools, low grade fever, and anorexia six weeks prior to admission. Endamoeba histolytica had been reported in the stools in an examination performed elsewhere, but the symptoms persisted despite anti-amebic therapy. In addition to these symptoms, two weeks prior to admission the patient had a gradual onset of edema, involving the ankles, buttocks, and scrotum. On admission, he was having twenty serosanguineous purulent stools a day.

On physical examination the patient was too asthenic to be weighed. Moderate pallor was present. Severe edema involved not only the four extremities, but also the scrotum, buttocks, neck, and face. There was a decubitus ulcer 3 cm. in diameter over the sacrum. Temperature ranged up to 100 F.

Pertinent laboratory findings are presented in Table 1. The serum albumin of 1.0 Gm. (Tiselius Method) is one of the lowest we have seen and undoubtedly accounted for the pronounced edema. The gamma globulin was 35 per cent above normal, being 1.17 Gm. The differential count on admission: neutrophils—93 per cent, lymphocytes—3 per cent, monocytes—4 per cent. The reticulocyte count was 8.7 per cent. Repeated stool examinations at the Cleveland Clinic were negative for E. histolytica.

TABLE 1

Test	Admission	4th hospital day	8th day	15th day
R.B.C.	3.5 million	5.8 million	5.6 million	5.4 million
Hemoglobin	9.0 Gm.	13.4 Gm.	13.4 Gm.	13.5 Gm.
W.B.C.	21,000	38,150	9,000	13,950
Serum albumin (Tiselius)	1.0 Gm.		2.75 Gm.	3.30 Gm.
Serum calcium	8.0 mg.			10.5 mg.

Barium enema examination showed involvement of all portions of the colon with chronic ulcerative colitis, suggesting multiple submucosal ulcerations and surrounding polypoid hyperplasia, and some involvement of the distal 5 to 10 cm. of the terminal ileum (fig. 1).

Proctoscopic examination showed diffuse edema with a slightly granular mucosa and minimal bleeding, but with much blood and pus coming from above.

The clinical progress of the patient was just as dramatic as the remarkable increase in the serum albumin. The temperature subsided to normal so that there was no fever after the seventh hospital day. By the eighth hospital day the generalized edema had completely disappeared. The number of stools decreased from twenty to two per day. The patient was ambulatory and was feeling well when he was discharged from the hospital on the seventeenth day of hospitalization. Five months later, his mother reported that there had been no recurrence of the diarrhea, his appetite was excellent, and he had gained 28 pounds. The treatment employed was as follows:

1. Nutrition. With the generalized edema and remarkably low serum albumin, it was evident that this patient required much food. His diet was increased to the maximum. The average caloric intake the first eight days was 1900 calories, while the second eight days the average intake was 3655 calories daily. Keeton et al[3] were able to keep patients in positive nitrogen balance despite surgical procedures that usually resulted in negative nitrogen balance for two weeks by forcing a high protein intake. These patients need a similar high protein intake.

2. Intravenous feedings of 1000 cc. of 6 per cent protein hydrolysate were given daily.

3. Four transfusions of 500 cc. each of whole blood were given the first week.

4. Vitamins. Crude liver extract in 2 cc. doses and 2 cc. of high potency vitamin B complex were given parenterally daily. In addition, he was given large amounts of vitamins A, C, D and K orally.

5. Antispasmodics and sedatives in the form of tincture of belladonna and the barbiturates were prescribed orally in an attempt to relax the colon.

6. Testosterone propionate was given parenterally in a dose of 25 mg. daily. This produced no masculinizing effect in this patient. The purpose of the endocrine therapy was to improve the nitrogen metabolism and to convert him from an obvious negative nitrogen balance to a positive one.

Several investigators[4] have shown that the administration of testosterone propionate to normal and debilitated persons reduces the urinary nitrogen

excretion and establishes a more positive nitrogen balance. This effect is believed to be one of increased protein anabolism, and was observed in patients with rheumatoid arthritis, nephrosis, uncontrolled diabetes, hyperthyroidism, non-specific ulcerative colitis and regional ileitis, and in normal patients on a starvation diet. The optimal dose appears to be 25 mg. daily from five to twenty-five days. Such a dose if continued for longer than twenty-five days may cause virilism; changes in the voice and hirsutism should be watched for in anyone receiving this therapy. Closure of epiphyses[5] may also occur, but is an effect of extended treatments (three to nine months or more). Testosterone propionate is an aid in improving the nitrogen metabolism in a desperately ill and debilitated patient.

Fig. 1. Barium enema examination in case 1 showing serrations and ulcerations along the descending colon and also involvement of ascending and transverse colon. The terminal ileum is not well shown on the photograph but was thought to be involved fluoroscopically.

7. Antibiotic and Chemotherapy. There is nothing specific about antibiotics in the treatment of these patients. However antibiotics may frequently reduce the secondary invaders and consequently reduce the inflammation of the colon.[6] From the second to the eighth hospital day, this patient received 0.5 Gm. of streptomycin twice daily, 300,000 units of penicillin twice daily, and 0.5 Gm. of sulfathaladine four times a day. It has been shown that aureomycin is effective against a wider range of bacteria than either streptomycin or penicillin or both together. Consequently, on the eighth hospital day the sulfathaladine, penicillin, and streptomycin were all discontinued, and 1.5 Gm. of aureomycin was given daily. We have been unable to find any reports in

the literature on the effect of aureomycin in ulcerative colitis. While it is difficult to determine the effectiveness of any one drug where so many therapeutic measures are employed, nevertheless with the institution of aureomycin therapy there was a coincidental increase in this patient's appetite and caloric intake.

Case 2. A woman, aged 30, was admitted to the Cleveland Clinic Hospital December 3, 1948. She gave a history of having had diarrhea for five weeks in 1940, a recurrence of the diarrhea with purulent serosanguineous stools in 1942 at which time a resection of the terminal ileum with ileo-transverse-colostomy was performed elsewhere. In July 1948 she had a recurrence of the diarrhea for which she was hospitalized at another hospital and given intensive supportive treatment. However, she failed to respond and an "emergency" ileostomy was performed. Following surgery, the patient continued to fail, having a toxic septic course with daily temperative to 102 F., secondary anemia, and severe loss of weight. She developed undermining of the skin about the ileostomy and a perineal fecal fistula. She was confined to another hospital from July until she was admitted to the Cleveland Clinic Hospital December 3, 1948.

On physical examination, the patient was extremely emaciated and asthenic and was too weak to be weighed. The temperature was 102 F., pulse was 110, weak and thready, and the blood pressure was 80/60. There was a large necrotic area in the abdomen measuring approximately 20 cm. in diameter, its base formed by the external oblique muscle into which emptied a fecal fistula. A left perineal fecal fistula was also present. The patient was placed on the seriously ill list. Her condition was too poor to permit any surgical procedure whatever.

Pertinent laboratory examinations on admission were: Hemoglobin was 9.0 Gm. There were 3,450,000 red blood cells and 6500 white blood cells per cu. mm. Serum albumin (Tiselius Method) was 2.44 Gm. Repeated stool examinations were negative for amebae and parasites, but positive for blood and pus.

The progress of this patient after the first week of treatment was striking. She had no further fever, her appetite and caloric intake improved greatly, the anemia was corrected, and the serum proteins became normal. The enormous defect in the abdominal wall gradually granulated in and healed by third intention. The abdominal fecal fistula closed spontaneously on the twenty-fifth day. The perineal fistula also closed spontaneously. The patient was discharged thirty-three days after admission to the hospital. Four months later, she had gained 29 pounds in weight, had only four to five stools a day, and appeared to be in excellent health. The treatment employed was as follows:

1. Nutrition. After the first eight days, this patient had an average caloric intake of 2600 calories per day. A low residue bland diet with over 100 Gm. of protein a day was used.

2. Intravenous feedings of 1,000 cc. of 5 per cent glucose in saline daily for the first three days, and 1,000 cc. of 6 per cent protein hydrolysate daily for the first twenty-one days were given.

3. Five blood transfusions of 500 cc. each were given in the first week of treatment.

4. Vitamins. Crude liver extract (2 cc.) and 2 cc. of high potency vitamin B complex were given parenterally daily, and liberal amounts of A, C, D, and K were given orally.

5. Symptomatic measures to control the diarrhea included antispasmodics (belladonna to tolerance), sedatives (phenobarbital), small amounts of paregoric, and hydrophilic colloids with kaolin and calcium carbonate.

6. Testosterone propionate was given parenterally in a dose of 100 mg. every other day for the first week, and 25 mg. every other day for the next two weeks. No masculinizing effect was observed.

7. Antibiotic and Chemotherapy. The patient was given 2 Gm. of streptomycin, 600,000 units of penicillin daily for the first twelve days. She also received 6 Gm. of sulfathaladine orally each of the thirty-three days she was in the hospital.

8. One of this patient's most difficult problems was the definite undermining of the abdominal wall, extending for a diameter of 20 cm. around the ileostomy. Healing was promoted by two measures. First, a glass cannula was inserted into the ileostomy, and continuous suction was applied, thus diverting the fecal stream away from the defect in the abdominal wall. Second, Pickrell's solution was applied to this area by means of gauze pads every twenty minutes day and night. Stiefel and Kelleher[7] have already reported on the value of Pickrell's solution in the management of skin excoriations associated with entero-abdominal fistula. Pickrell's solution is a solution of 2.5 per cent sulfadiazine in ethanolamine and distilled water.

Discussion

A brief report is presented of 2 patients critically ill with ulcerative colitis. Both made a dramatic response to intensive treatment. The treatment used in each case is outlined and we feel that all of the measures employed contributed to the recovery of these patients.

Several relatively new therapeutic aids seemed to be of help. Testosterone administered parentally seemed to help the nitrogen metabolism of both patients. Aureomycin appeared to be beneficial in the one patient to whom it was given. The use of a glass cannula to divert the fecal stream and the application of Pickrell's solution was of value in the healing of a large abdominal wall defect in the other patient.

The treatment of a patient seriously ill with acute fulminating ulcerative colitis must be individualized for that patient, and no stereotyped treatment can be set forth for all cases. Other measures, such as oxygen inhalations (Bargen), the use of a Miller-Abbott tube with the tip in the ileum as a "medical ileostomy" as described by Machella and Miller,[8] the use of sulfasuxidine or sulfathaladine retention enemas,[9] the continuous intravenous administration of protein hydrolysates, the treatment of allergy and other measures have all proven to be of value in certain cases and are indicated in some patients. These additional measures were unnecessary in the 2 patients presented.

References

1. Bargen, J. A., Lindahl, W. W., Ashburn, F. S. and Pemberton, J. de J.: Ileostomy for chronic ulcerative colitis. Ann. Int. Med. **18**:43-56 (Jan.) 1943.
2. Cattell, R. B.: Surgical treatment of ulcerative colitis. Gastroenterology **10**:63-66 (Jan.) 1948.
3. Keeton, R. W. et al: Convalescence: Study in physiological recovery of nitrogen metabolism and liver function. Ann. Int. Med. **28**:521-552 (March) 1948.

4. Kenyon, A. T.: Conferences on bone and wound healing. Josiah Macy, Jr. Foundation. p. 59-69, 18-19, 75-76, 49-53 (Dec.) 1942; p. 128-141, 169-183 (March) 1943; p. 127-137 (June) 1943.

5. McCullagh, E. P. and McGurl, F. J.: Effects of testosterone propionate on epiphyseal closure, sodium and chloride balance and on sperm counts. Endocrinology **26**:377-384 (March) 1940.

6. Block, M. and Pollard, H. M.: Chemotherapy and antibiotics in chronic ulcerative colitis. Gastroenterology **10**:46-58 (Jan.) 1948.

7. Stiefel, R. A. and Kellcher, G. T.: Pickrell's solution in management of skin excoriations associated with enter-abdomir.al fistula. J. Michigan Soc. **47**:1240 (Nov.) 1948.

8. Machella, T. E. and Miller, T. G.: Treatment of idiopathic ulcerative colitis by means of "medical ileostomy" and orally administered protein hydrolysate-dextri-maltose mixture. Gastroenterology **10**:28-45 (Jan.) 1948.

9. Collins, E. N. and Hewlett, J. S.: Succinyl sulfathiazole (sulfasuxidine) in treatment of chronic ulcerative colitis. Gastroenterology **7**:549-554 (Nov.) 1946.

STRUMA LYMPHOMATOSA

Case Report

W. S. DEMPSEY, M.D., R. S. DINSMORE, M.D., and JOHN B. HAZARD, M.D.

Departments of General Surgery and Pathology

STRUMA LYMPHOMATOSA is an uncommon lesion of the thyroid gland. Diagnosis prior to operation is comparatively rare as are complete preoperative studies. In the case of this disease reported here the diagnosis was made preoperatively and special studies were carried out.

Case Report

A slightly obese uniparous white woman, aged 58 years, was admitted to the Cleveland Clinic Hospital on January 16, 1949. Her past history did not reveal anything significant. The present illness, however, dated from 1941 at which time she had had all her teeth extracted. Shortly thereafter she began to have transient episodes of a constricting sensation in her throat accompanied by a mild dysphagia. Concomitantly she experienced aching in the low anterior cervical region with slight radiation laterally. These incidents lasted only a matter of minutes, occurred about six or eight times a year and were not accompanied by either fever or severe pain. She had gained thirty pounds in the past seven years. A thorough study of the patient had been made in 1942. At that time her thyroid was palpable but not enlarged. No history of hyperthyroidism was elicited. Esophagram, chest roentgenogram, esophagoscopy, and laryngoscopy were also normal.

At the time of examination on January 16, 1949 her temperature was 98 F. The pulse rate was 72, respirations 21, and blood pressure 150 systolic, 90 diastolic. The patient was rather short, well developed and moderately obese. The thyroid gland showed definite diffuse enlargement with slight nodularity. No tenderness was elicited. The vocal cords appeared and moved normally. Except for the enlarged thyroid the physical examination was normal.

Examination of the urine showed no abnormality. The hemoglobin was 12 Gm. and the white cell count 8100. The blood serology was negative. A fasting blood sugar was 98 mg. per cent.

A gastric analysis showed a free hydrochloric acid of 5° and a total acidity of 15°. The basal metabolic rate was minus 10 per cent. A sedimentation rate was 0.9 (normal 0.45).

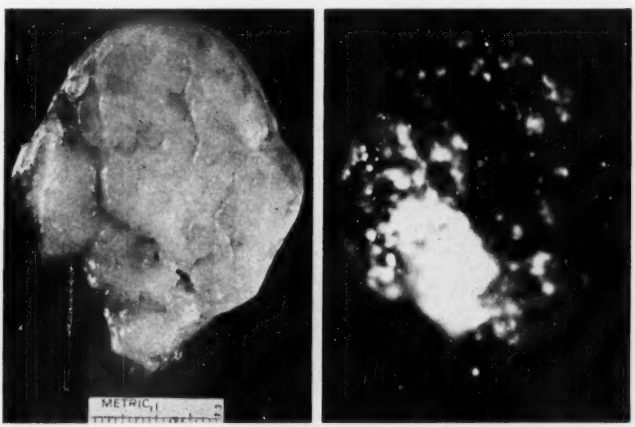
A roentgenogram of the chest revealed deviation of the trachea to the left. Although a soft tissue mass could not be definitely visualized, thyroid enlargement could not be excluded. A tracer dose of 0.4 mc. I^{131} was given January 17, 1949. Two hours later a 20 per cent uptake was recorded over the thyroid area. The preoperative diagnosis was struma lymphomatosa.

A right lobectomy was performed on January 17, 1949 under local anesthesia supplemented by gas oxygen ether. The patient's convalescence was uneventful and she was discharged six days after operation.

Pathology. Grossly the specimen consisted of the greater portion of the right lobe of the thyroid which weighed 30 Gm. and measured 7 by 6 by 4 cm. The capsule was thin, smooth and glistening and there was no muscle adherent. On the posterior surface there was an elongated depression (representing the area of tracheal compression). The tissue was of firm rubbery consistency and

on section was diffusely white and yellowish-white with a slightly bulging surface and a few irregular, slightly depressed septations (fig. 1a).

Microscopically practically the entire lobe was formed by fairly dense fibrous tissue trabeculations and masses of lymphocytes and plasma cells infiltrating lobules of acidophilic thyroid follicles. The connective tissue occurred as broad trabeculations of dense character (fig. 2a) and interlobular location and as a diffuse interfollicular increase of more loosely arranged type. The lymphocytes and plasma cells densely infiltrated the interfollicular zones corresponding with the thyroid plates, the lymphocytes replacing other tissues in microscopic areas and including large and active lymph follicles (fig. 2b). Foreign body giant cells were rare. A few histiocytes existed in or near a follicle but there was no tubercle formation. There was a definite reduction in epithelial elements. The follicles were of small to medium size and formed chiefly by large acidophilic cells, 10 to 20 microns in diameter, cuboidal or polyhedral in shape, and with abundant finely granular cytoplasm. Occasional bizarre giant nuclear forms were present. Follicular lumina contained a moderate amount of pale staining colloid. There were scattered small, irregular islands of darker staining epithelial cells, 5 to 12 microns wide, polyhedral in shape which were large centrally and smaller marginally in stratified or palisade arrangement. Blending with the acidophilic thyroid tissue were irregular foci of follicles with the pale staining granular neutrophilic cuboidal epithelial cells, 3 to 7 microns in diameter, forming lumina of moderate size containing colloid. The thyroid capsule showed a patchy infiltration by lymphocytes, without increase in connective tissue; it was well demarcated from the perithyroid tissues which were of typical character and density.

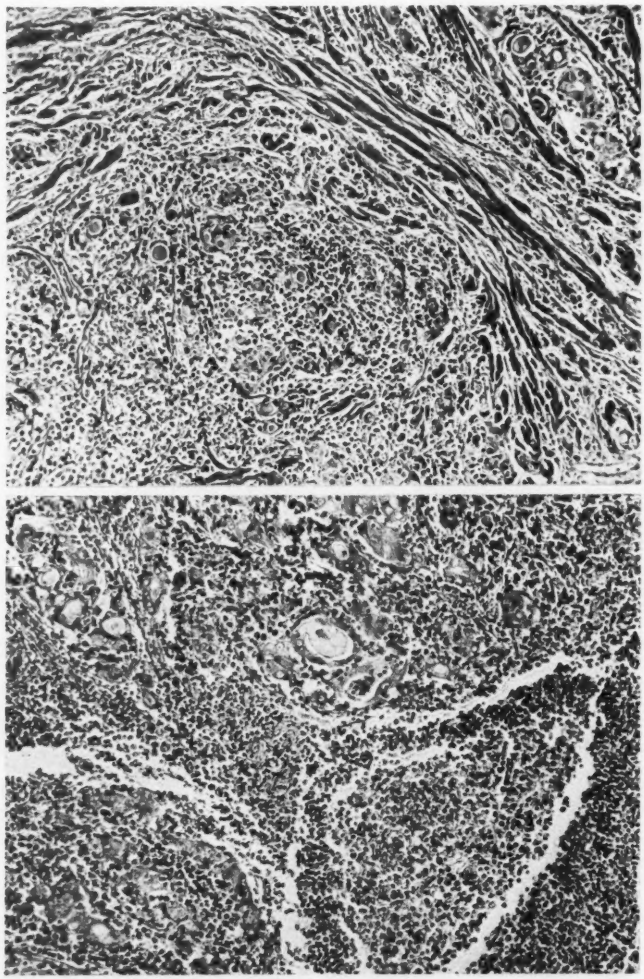


(a) (b)

Fig. 1. (a) Gross specimen showing irregular, coarsely lobulated bulging surface; (b) gross radioautograph. Scattered small irregular light foci and the white conglomerate patch indicate zones of radioactivity.

The pathologic diagnosis was struma lymphomatosa (Hashimoto) with focal squamous metaplasia.

(a)



(b)

Fig. 2. (a) Sclerosis, surrounding and partly extending into thyroid plate; small thyroid follicles with oxyphilic epithelium and separated by cellular infiltration of plate; (b) lymph nodule formation and dense cellular infiltration (plasmacyte and lymphocyte) in thyroid plates, separating small oxyphilic follicles.

Radioautographs. A radioautograph of a thin section of the gross specimen revealed small scattered foci and one conglomerate patch of radioactivity (fig. 1b). Contact radioautographs of microscopic sections of the specimen used for the gross demonstration, revealed absence of radioactivity in the zones with oxyphilic epithelium. Scattered foci of radioactivity were found in the few zones with follicles formed by neutrophilic cuboidal epithelial cells.

Summary

The clinical history of this case is typical inasmuch as the symptoms were vague, poorly defined, and the onset insidious. The gastric analysis revealed only 5° free hydrochloric acid. Graham[1] reported anacidity or hypoacidity in 6 of 14 cases of struma lymphomatosa.

The basal metabolic rate in this patient was minus 10 per cent. In 14 cases reported by Crile[2] the average metabolic rate was minus 8 per cent. The sedimentation rate was 0.9 (normal 0.45). The uptake of radioactive iodine was below that of a normal thyroid gland. Because the diagnosis was confirmed after removal of the right lobe no further surgery was performed. Conservative surgery with the object of decompression only has been recommended by Crile[2] and by Marshall et al.[3]

References

1. Graham, A.: Struma lymphomatosa (Hashimoto). Trans. Am. A. Study Goiter, p. 222-251, 1940.
2. Crile, G., Jr.: Thyroiditis. Ann. Surg. **127**:640-654 (April) 1949.
3. Marshall, S. F., Meissner, W. A., and Smith, D. C.: Chronic thyroiditis. New England J. Med. **238**:758-766 (May 27) 1948.

RHEUMATIC BRAIN DISEASE AS A CAUSE OF CONVULSIONS

J. F. WHITMAN, M.D., and LOUIS J. KARNOSH, M.D.
Department of Neuropsychiatry

THE classical symptoms of acute rheumatic fever have been recognized for many years, but the other manifestations of this protean process were long interpreted as simply sequelae of the acute infection. It is now universally agreed that the endocardium harbors primary lesions,[22] but it is not so commonly realized that the brain may be similarly affected. Certainly the details of the etiology of rheumatic fever are not yet understood. It does appear, however, that the disease is basically an inflammatory condition of fibrous connective tissue. As such the brain cannot be excluded as a potential site. Indeed, rheumatic lesions have been found in lungs,[2,28] kidneys,[10,24] spleen, ovaries,[24] testes,[24] pancreas,[24] coronary arteries,[12,15] in peripheral arteries[24] and in the brain.

Many theories of the pathogenesis of brain complications have been proposed; most have assumed that the lesions were secondary to rheumatic heart disease. Some investigators have said that cardiac valvular lesions brought on circulatory changes in the brain causing stasis and ischemia. Evidence against this theory is the fact that the majority of patients with rheumatic brain disease, including those presented here have no history of congestive heart failure. It has also been conjectured that minute emboli may detach from rheumatic vegetations and lodge in vessels of the brain, but the cohesive properties of these vegetations speak against this mechanism. It is true, in patients with mitral stenosis and auricular fibrillation, mural thrombi may beget emboli, but pathologists deny that such emboli form foci for the endarteritic changes which characterize rheumatic brain disease. Of the cases to be presented in only one was there suspicion of an irregularity of cardiac rhythm.

From statistics, even after allowing for the distortions which commonly arise in this approach, several striking inferences can be drawn. Bruetsch[20] reported a 5 per cent incidence of rheumatic heart disease in 500 consecutive and unselected necropsies from a mental hospital, and a somewhat higher figure clinically in all admissions to that hospital over a recent two year period. This is compared to a general incidence in the United States of less than 1 per cent.[14] More dramatic than this, however, the same observer, reported that in his last 30 consecutive necropsies on patients with rheumatic heart disease, he found only one brain in which rheumatic lesions could not be found.

In chronic cases, the brain pathology has been described as basically an obliterating proliferative endarteritis[4] which is most common in small meningeal and cortical vessels and is accompanied subsequently by softening of the cortex. There is no typical distribution of the lesions; usually only short segments of small vessels are involved, the larger vessels of the basal ganglia are

not commonly affected. Neuberger's[19] necropsy studies of acute cases revealed the presence of small fibrocytic nodules in meningeal vessel walls together with patchy fibrosis and lymphocytic infiltration into the meninges. Others have drawn attention to the similarity between the endarteritis in the cortex and in rheumatic myocardium.

The histopathology is by no means specific and a differentiation from syphilitic endarteritis cannot be made with a microscope. A diagnosis can be reached only after finding other rheumatic lesions in the body and after excluding syphilis so far as is clinically possible. Even then, other possibilities for consideration must include thromboangiitis obliterans, lupus erythematosus and periarteritis nodosa, the latter being so similar microscopically that Fahr[10] has suggested that rheumatic vascular lesions may contribute to its pathogenesis. In acute rheumatic fever, the microscopic changes in the brain are much the same as those found in other severe infections or toxemias.[27] Aschoff nodules are not found in the brain, possibly, because there is relatively so little connective tissue as Boyd[1] suggests or because Aschoff nodules represent a specific response in the myocardium.

Rheumatic brain lesions have been incriminated as precursors of a large number of neurologic and psychiatric aberrations.[3,5,6,8,9,11,13,23,26] The degree to which clinical manifestations develop appears to depend on the size, number and locale of the foci. The nature of the symptoms is further determined by the age and personality of the patient at the time of involvement. In childhood, deviations range from mild behavior disorders to pronounced mental deficiency. Young adults tend to develop schizophrenic reactions,[6] while involutional melancholia and manic depressive psychoses are common in older age groups. The literature reveals that nearly any psychiatric syndrome may be produced; there is no particular psychopathologic content, and one is frequently unable to distinguish psychogenic from organic etiologies.

Although suggested in 1843,[18] it has only recently been recognized that chronic rheumatic infection may cause epilepsy. Walker[25] in 1936, did not include rheumatic brain disease among more than 70 causes of convulsions. Seizures resembling cryptogenic epilepsy in patients with rheumatic heart disease were reported profusely in the French literature of the 1930's. Foster[11] has shown that the incidence of seizures is two and one half to seven times higher in patients with rheumatic heart disease than in large control groups. It is probable that many cases are diagnosed as idiopathic epilepsy which are actually due to organic brain disease of rheumatic etiology. Bruetsch[5] has reported 3 such cases which presented rather extensive heart and brain disease at necropsy.

Though we lack pathologic confirmation of diagnoses coded as rheumatic brain disease in our files, we feel that the data yield several clinically significant points. These cases include 5 patients with histories of recurrent generalized convulsive seizures, several of whom had previously been diagnosed as idiopathic epilepsy. In none of these patients was there any suspicion that syphilis, trauma, expanding intracranial lesion, arteriosclerosis, alcohol, kidney failure or other epileptogenic factors were of significance in causing the dis-

order. There was a remote family history of epilepsy in only 1 case. Each patient had clinically demonstrable rheumatic heart disease; and all had electro-encephalograms which were abnormal, but which revealed no single unique characteristic feature.

The average age of these patients was 45.6 years and the onset of their seizures had occurred at an average age of 38.6 years. None had had convulsions before they were 34 years old. Studies with large groups of cases[11,16,17,21] indicate that the incidence of idiopathic epilepsy, with seizures first appearing after the age of 20, is low, and is practically negligible when the onset occurs past 30. Thus the diagnosis of idiopathic epilepsy in patients over 20 years old should be made only after all other factors have been exhaustively eliminated. We feel that we have, in these cases, ruled out all known organic factors exclusive of rheumatic brain disease to which we believe these seizures have been due.

Three of these 5 patients had a past history of a definite migratory polyarthritis or chorea; their convulsive seizures, however, did not begin until ten, twelve and thirty-two years later. This latent period has also been noted by other observers and it may be explained by the fact that the arteritis in the brain develops during an asymptomatic period while the patient is enjoying good general health (table).

TABLE

Case Number	Age of Patient	Age of Onset of Seizures	Age at Time of Arthritis Symptoms	Latent Period
1	52	42	30	12
2	45	34	....	....
3	41	40	30	10
4	36	35	....	....
5	54	42	10*	32
Average	45.6	38.6		

*Approximate

Demonstrating the Chronology of Events in the Development of Rheumatic Epilepsy

Case Reports

Case 1. A 52-year-old white woman first came to Cleveland Clinic on June 11, 1947. She stated that she had begun to experience recurrent convulsive seizures in 1937. An objective history revealed that during these attacks, which usually were without premonitory symptoms, chronic movements began in the head and then rapidly became generalized and frequently tonic. Excess salivation was noted and she occasionally bit her tongue. Convulsions were of three to four minutes' duration, and postconvulsive confusion lasted about twenty minutes; they were occasionally diurnal but much more commonly nocturnal. The frequency had been quite variable, and intervals between convulsions had varied from three weeks to six months since their onset.

There was no familial history of epilepsy or migraine, and the past history was not essentially contributory except that she had had a migratory polyarthritis twenty-two years

before, with an immediately subsequent diagnosis of "heart involvement." There had been no trauma prior to 1937 and no history of venereal disease.

Physical examination revealed an oral temperature of 99.2 F., a blood pressure of 116/64, and a pulse rate of 80. The heart was normal in size and the rhythm was regular. There was a grade 3 blowing diastolic murmur along the left border of the sternum and grade 1 apical systolic murmur. There were no thrills and no gallop rhythm. The Cardiology Department reported these findings as indicating the presence of rheumatic heart disease with aortic insufficiency. The rest of the physical examination, including a neurologic survey was negative.

In the laboratory, Wassermann and Kahn reactions were negative, a three hour postprandial blood sugar determination was 100 mg. per 100 cc., the hemoglobin estimation was 12.5 Gm. per 100 cc., and the leukocyte count was 7,700 per cu. mm. Skull and chest x-rays were essentially negative. An electro-encephalogram showed little normal alpha activity, generalized low voltage and indistinct waves, and some irregular slow waves from the right parietal region which were not found on the left. It was interpreted as "An abnormal electro-encephalogram which is more suggestive of an organic brain disease than idiopathic epilepsy."

Case 2. A 45-year-old white woman, was examined at the Cleveland Clinic on April 4, 1947 at which time her chief complaint was "convulsions," the first of which had occurred eleven years before. Loss of consciousness always occurred without premonition, and was followed by a generalized clonic convulsion lasting for approximately one minute and unconsciousness lasting for fifteen minutes. There was no characteristic time of day for the occurrence, and the frequency though variable was generally increasing and the tendency to appear during the week preceding menstruation was striking.

One paternal uncle had been epileptic, otherwise her past history was not significant.

On physical examination, temperature was 98.6 F., pulse 80, and blood pressure 130/74. Her heart was slightly enlarged to percussion, there was a grade 3 blowing systolic murmur at the apex and a grade 2 systolic murmur at the aortic area. The diagnosis in the Cardiology Department was rheumatic heart disease with mitral insufficiency and probably aortic stenosis. The physical examination was otherwise negative.

Cerebrospinal fluid and serologic examinations were negative in 1946. An x-ray of the skull was normal. The electro-encephalogram showed a generalized slow dysrhythmia with frequencies of 5 to 7 per second and voltages to 125 microvolts. The interpretation was "An abnormal encephalogram with no evidence of a focal cortical lesion."

Case 3. A 41-year-old white man, was first seen at Cleveland Clinic on February 5, 1948, at which time he reported that during the past year he had experienced two nocturnal convulsive seizures. He had been subjectively unaware of these attacks except that he experienced a generalized muscular soreness the next day.

No family history of epilepsy or migraine was elicitable, but the past history revealed that the patient had experienced a rather severe and extensive polyarthritis in 1937, since which time he has been told of the presence of a "heart murmur." The detailed history was not additionally significant.

Physical examination of the heart disclosed a grade 4 apical systolic murmur at the apex which was interpreted by the Cardiology Department as indicating rheumatic heart disease with mitral insufficiency.

Laboratory studies included negative Wassermann and Kahn tests, a fasting blood sugar level of 84 mg. per 100 cc., a sedimentation rate of 0.65 mm. (0.45 mm.-normal), a hemoglobin estimation of 14.5 Gm. per 100 cc., and a leukocyte count of 6200 per cu. mm. X-rays of the chest and skull were negative. The electro-encephalogram showed a poor alpha pattern, low voltage, and some focal slow waves from the right frontal region. It was interpreted as "An abnormal electro-encephalogram with some suggestion of localization in the right frontal region."

Case 4. A 36-year-old white man was first seen at Cleveland Clinic on February 4, 1947. He had suffered recurrent grand mal convulsive seizures for the past year. There had been 5 episodes all of which, except one, had been nocturnal, each of which had lasted

about five minutes and had been followed by mental confusion and apathy. There was no family history of epilepsy or migraine, no past history of rheumatic fever.

Physical examination showed a temperature of 99.4 F., a pulse of 100, and a blood pressure of 104/64. The heart was enlarged to percussion; there was a grade 4 diastolic cresendo murmur and thrill at the apex. These findings were interpreted as those of rheumatic heart disease with mitral stenosis. There was nothing additionally significant in the physical examination.

The Wassermann and Kahn tests were negative, the blood sugar was normal. There was 14.5 Gm. of hemoglobin per 100 cc., and the leukocyte count was 14,600 per cu. mm. A skull x-ray was negative. The electro-encephalographic record showed no definite alpha pattern and low voltage waves. It was interpreted as "A borderline record with no definite evidence of epilepsy nor of a focal cortical lesion."

Case 5. A man, aged 54, was first seen on September 16, 1941. He gave a history of recurrent grand mal seizures for twelve years. There was a past history of rheumatic fever and a "heart leak" first noted in childhood. His physical examination included the findings of an apical diastolic murmur and an irregular irregularity which were interpreted as indicating rheumatic heart disease with mitral stenosis and auricular fibrillation. The remainder of the physical examination was not contributory.

The electro-encephalogram revealed a dysrhythmia most evident in the left frontal area where a convulsive focus was indicated.

Summary

Of the criteria for the diagnosis of rheumatic brain disease prior to necropsy, the clinical demonstration of rheumatic heart disease is most imperative and a history of acute rheumatic fever is desirable. It is even more difficult to evaluate inflammatory activity in the central nervous system than in the heart. Febrile responses are infrequent, but correlation of the activity with rise in the sedimentation rate and leukocyte count has been reported. Electroencephalography appears to be of no specific diagnostic value; the records in the cases reported were abnormal but showed no deviation which might be considered in any way pathognomonic of the lesion.

An accurate history stressing time relationships is of decided importance. Knowledge of the age of the patient at the time of the onset of his symptoms is a valuable aid in distinguishing between seizures due to rheumatic brain disease and those included in the catch-all classification of idiopathic epilepsy. The latent period between the active polyarthritis and the appearance of symptoms indicating central nervous system involvement is observed so commonly that its significance cannot be doubted, though its explanation is far from clear.

Since chronic rheumatic processes are frequently insidious and, at times, even asymptomatic, they may cause much more psychiatric and neurologic illness than suspected. On the other hand, we should guard against taking advantage of the admittedly vague aspect of the diagnosis in the attempt to classify disease beyond our science and art. A conservative consideration of rheumatic brain disease along with other causes of convulsions is desirable.

References

1. Boyd, William: The Pathology of Internal Diseases (Philadelphia: Lea and Febiger, 1944).

2. Brenner, O.: Pathology of vessels of pulmonary circulation. Arch. Int. Med. **56**:1189 (Dec.) 1935.
3. Bruetsch, W. L.: Late cerebral sequelae of rheumatic fever. Arch. Int. Med. **73**:472-476 (June) 1944.
4. Idem: Rheumatic endarteritis of cerebral vessels; sequel of rheumatic fever. Trans. Am. Neurol. A. **68**:17-20, 1942.
5. Idem: Rheumatic epilepsy; sequel of rheumatic fever. Am. J. Psychiat. **98**:727-732 (March) 1942.
6. Idem: Chronic rheumatic brain disease as possible factor in causation of some cases of dementia praecox. Am. J. Psychiat. **97**:276-296 (Sept.) 1940.
7. Idem: Histopathology of psychoses with subacute bacterial and chronic verrucose rheumatic endocarditis. Am. J. Psychiat. **95**:335-346 (Sept.) 1938.
8. Idem: Rheumatic brain disease; late sequel of rheumatic fever. J.A.M.A. **134**:450-454 (May 31) 1947.
9. Dublin, W. B.: Pathologic lesions of brain associated with chronic rheumatic endocarditis and accompanied by psychosis. Dis. Nerv. System **2**:390-393 (Dec.) 1941.
10. Fahr, T.: Nephrosclerosis. Deutsches Arch. f. klin. Med. **134**:366 (Dec.) 1920.
11. Foster, D. B.: Association between convulsive seizures and rheumatic heart disease. Arch. Neurol. and Psychiat. **47**:254-264 (Feb.) 1942.
12. Gross, L., Kugel, M. A., and Epstein, E. Z.: Lesions of coronary arteries and their branches in rheumatic fever. Am. J. Path. **11**:253-280 (March) 1935.
13. Guttmann, E.: On some constitutional aspects of chorea and on its sequelae. J. Neurol. and Psychopath. **17**:16-26 (July) 1936.
14. Hedley, O. F.: Rheumatic heart disease; National health problem. Proc. A. Life. Insur. M. Dir. Amer. (1938) .**25**:163-201, 1939.
15. Karsner, H. T. and Bayless F.: Coronary arteries in rheumatic fever. Am. Heart J. **9**:557-585 (June) 1934.
16. Lennox, W. G., and Cobb, S.: Epilepsy (Baltimore: Williams and Wilkins Co., 1928).
17. Lennox, W. G.: Science and Seizures (New York: Harper and Brothers, 1941).
18. Littré, cited by Oddo, C. and Mattei, C.: L'épilepsie cardiaque. Gaz. d. hôp. **92**:1005 (Oct. 25); 1037 (Nov. 1) 1919.
19. Neuberger, K. T.: Brain in rheumatic fever. Dis. Nerv. System **8**:259-262 (Aug.) 1947.
20. Ninety-Eighth Annual Report of the Central State Hospital, Indianapolis, Ind. 1946.
21. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization (Baltimore: Charles C Thomas, 1941).
22. Sacks, B.: Pathology of rheumatic fever; critical review. Am. Heart J. **1**:750-772 (Aug.) 1926.
23. Van der Horst, L.: Rheumatism and Psychosis, Digest of Neurology and Psychiatry. The Institute of Living, Series No. 15 (July) 1947.
24. Von Glahn, W. C. and Pappenheimer, A. M.: Specific lesions of peripheral blood vessels in rheumatism. Am. J. Path. **2**:235-249 (May) 1926.
25. Walker, A. E.: Convulsive seizures in adult life. Arch. Int. Med. **58**:250-268 (Aug.) 1936.
26. Warren, H. A. and Chornyak, J.: Cerebral manifestations of acute rheumatic fever. Arch. Int. Med. **79**:589-601 (June) 1947.
27. Winkelman, N. W., and Eckel, J. L.: Endarteritis of small cortical vessels in severe infections and toxemias. Arch. Neurol. and Psychiat. **21**:863-875 (April) 1929.

AMOEBIC HEPATIC ABSCESS WITH BRONCHOHEPATIC FISTULA

Report of a Case

ARTHUR G. MICHELS, M.D., H. S. VAN ORDSTRAND, M.D., and E. N. COLLINS, M.D.

Departments of Cardiorespiratory Disease and Gastroenterology

PLEURALPNEUMONIC involvement comprises the most frequent complication of amoebic hepatic abscess. The majority of the cases result from rupture or direct extension of the liver abscess through the diaphragm into the pleural cavity. The diagnosis of hepatic amebiasis and possible concomitant pulmonary complications depends primarily upon the awareness of the great possibility of liver involvement following amoebic colon infections. The following case report is an example in which, because of the high index of suspicion, the diagnosis of amebiasis was initially made. In this patient bronchohepatic fistula developed from an amoebic liver abscess and the patient dramatically recovered on a regimen of antiamoebic treatment and closed drainage.

Case Report

A 54-year-old man of Italian descent when first examined at the Cleveland Clinic was complaining of right chest pain and fever of two months' duration. For the previous thirty years, the patient had noticed occasional loose stools but had had no other symptoms until the onset of his acute illness. Two months before examination, he had noticed constant dull right-sided lateral neck and shoulder pain accompanied by fever; this pain was aggravated by inspiration, coughing, or straining at stool. He had felt fatigued and warm, perspired a great deal. He had lost 24 pounds since the onset of his acute illness and was profoundly weak. A few days after the initial chest pain, he began to have daily diarrhea with two to four watery stools which did not contain bright blood or mucus. For the four weeks previous to the initial examination, anorexia was severe and the patient suffered from recurrent insomnia, eructation, epigastric fullness, and slight dyspnea. At the time of hospital admission, he was having paroxysms of coughing with the expectoration of blood-stained sputum. A determination of the time of onset of this hemoptysis could not be accurately established.

The patient appeared acutely ill. The temperature was 101.2 F., the pulse 100, and the respirations were 38 per minute. The blood pressure was 120 systolic, 70 diastolic. There was diminished respiratory excursion of the right chest with decreased resonance, tactile and vocal fremitus at the right lung base. Breath sounds in this area were diminished and there were frequent paroxysms of coughing with production of chocolate colored and blood-tinged sputum. The heart was essentially normal. The liver edge was barely palpable under the right costal border and was moderately tender. The left inguinal canal was dilated and filled with a large reducible hernia sac. Rectal and neurologic examinations disclosed no abnormalities.

The initial blood count was 4,100,000 red cells, hemoglobin of 10.5 Gm., and 16,450 white cells of which 90 per cent were neutrophils. The blood Wassermann and Kahn tests were negative and the urinalysis was normal. Total protein was 6.6 Gm. per 100 cc. with a reversal of the normal albumin globulin ratio: 2.8 Gm. albumin to 3.8 Gm. of globulin. Thymol turbidity was 1.6 units and cephalin flocculation test was equivocal. Bromsulfalein

test showed 24 per cent retention in thirty minutes. Icteric index was 4.0. Examination of the chocolate colored sputum was negative for tubercle bacilli, spirochetes, fungi, and amoebae. Sputum culture revealed non-hemolytic streptococci and N. catarrhalis. On five successive warm stool examinations occult blood test was positive several times but no amoeba were ever found.

The proctosigmoidoscopic examination revealed multiple discreet, punched out ulcers 3 to 5 mm. in diameter in the rectosigmoid colon at a distance of 10 to 15 cm. from the anal sphincter. Smears from the bases of the ulcer beds showed many amoebae which were suggestive in appearance of Endamoeba histolytica and in the warmed preparation, the motile vegetative forms of Endamoeba histolytica were positively identified.

Initial roentgen studies of the chest (fig. 1) demonstrated a large, smoothly outlined triangular mass in the right lower lung field. Films two days later showed a pleural effusion obscuring the lower two-thirds of the right lung (fig. 2). Stereoscopic films of the liver demonstrated immobilization of the right diaphragm. A diffuse inflammatory process of the entire colon with the most pronounced changes in the cecum and ascending colon was shown by barium enema (fig. 3).

On the second day in the hospital, a bronchoscopy was done. A considerable amount of thick brown mucus was found to be coming from the right middle and lower lobe bronchi with no evidence of bronchial obstruction or neoplasm. The two smears made from bronchial secretions were negative for tumor cells. On the following day, a thoracentesis was done in the sixth anterior interspace in the anterior axillary line with a total of 1800 cc. of chocolate colored or anchovy sauce fluid aspirated. Laboratory examination of this fluid was negative for tubercle bacilli, fungi, spirochetes, and amoeba. The specific gravity was 1.027 and the white cell count 62,000; all cells found were neutrophils.

Upon hospital admission, the patient was placed on intramuscular penicillin, 50,000 units every three hours until the diagnosis was established of intestinal amebiasis with hepatic abscess and pleural-pulmonary involvement. Following one day's treatment with penicillin, the patient's temperature fell to 100 F., and a few hours after specific antiamoebic treatment was begun, the patient became afebrile and remained so during the remainder of his hospital stay. The antiamoebic therapy used was as follows: The intramuscular injection of emetine

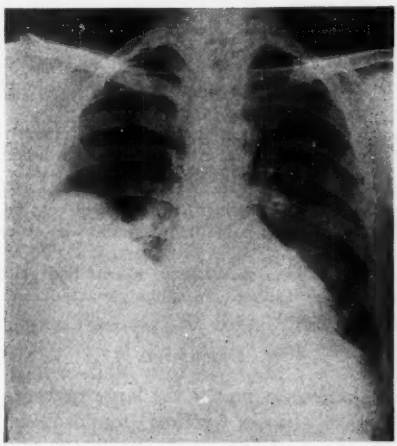


FIG. 1. Initial chest film showing large smoothly outlined triangular mass in right lower lung field.

hydrochloride 0.065 Gm. (1 grain), daily for six days and at the same time, one 0.25 Gm. carbarsone capsule given orally twice daily until twenty capsules had been used, followed by oral administration of diodoquin tablets 0.21 Gm., three tablets being given three times daily until a total of one hundred tablets were used.

The patient's response to antiamoebic therapy was immediate and his general condition improved with the gradual return of appetite, disappearance of chest pain and productive cough, cessation of diarrhea, and gradual clearing of the right chest as judged by chest films and physical findings. An additional 800 cc. of chocolate milk fluid was removed on the eighth hospital day by thoracentesis. During the first four days following hospital admission, the recurrent cough gradually became less productive of brown colored sputum indicating the closure of the bronchohepatic fistula. By the seventh hospital day, the patient's occasional dry cough was non-productive. Electrocardiogram remained normal after completion of the six-day course of emetine hydrochloride and there was no clinical evidence of peripheral neuritis. White cell count was 11,000 at this time. A week after initiation of specific treatment, there were fewer rectosigmoid ulcers found on proctosigmoidoscopic examination

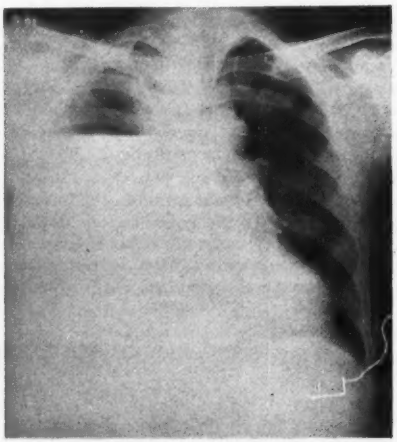


FIG. 2. Chest film taken two days after initial examination demonstrating a pleural effusion obscuring the lower two-thirds of right lung.

and these lesions showed evidence of healing. At the time of hospital discharge on the eighteenth hospital day, the liver was not palpable and there was no tenderness over the right upper quadrant.

Examination three months later showed the patient had gained 27 pounds and was symptom free. Roentgen studies disclosed no active pleural disease or free fluid. Residual right base pleural scarring was moderate.

Discussion

Amoebic hepatic abscesses comprise the large percentage of liver abscesses. In 287 patients with liver abscess, Oschner[1] found 63 per cent were amoebic in origin, and the remaining 37 per cent non-amoebic. Payne[2] reported liver abscesses in almost 3 per cent of 1000 cases of intestinal amebiasis. The diagnosis is not always easy to make as neither symptomatology or liver function

studies are pathognomonic but are merely suggestive of amoebic liver disease. Excessive indulgence in alcohol is believed to be the most important predisposing influence in favoring the development of amoebic hepatitis and liver abscess.

Amoebic hepatitis is the result of invasion of the liver by the amoebae through one of three possible routes: 1. by direct extension through the bowel wall, peritoneal cavity, and the capsule of the liver; 2. by lymphatic route, and 3. through the portal vein. The amoebic liver abscess contents have a characteristic appearance in non-infected cases. In the early stages, the abscess material is viscid, glary and semi-transparent; later, the contents become less viscid and with the mixture of blood, assume a yellow-red or chocolate brown color. This material has been given many terms and commonly is described

FIG. 3. Barium enema demonstrating the diffuse inflammatory process of entire colon.

as anchovy sauce or chocolate milk material. The formation of a well defined wall of connective tissue demarcates the abscess cavity and amoebae can be found throughout the peripheral abscess wall and frequently can be observed invading the surrounding liver parenchyma. Calcification of amoebic hepatic abscess is rare.

The amoebic hepatic abscesses are characteristically single and occur in the right lobe near the dome of the liver or near the inferior surface next to the hepatic flexure of the colon. The predominance of right liver involvement is closely related to the high incidence of amebiasis in the cecum and ascending colon. Venous drainage of the right colon is chiefly into the right lobe of the liver and is cited as cause for the great frequency of right-sided liver abscesses reported variously as 55 to 97 per cent. Multiple abscesses are present in less than 50 per cent.

Pleuralpulmonary complications of amoebic liver abscess occur in approximately 15 per cent. In a study of 2490 cases of amoebic hepatic abscess, Ochsner[3] found pleural complications occurring in 7.5 per cent and the pulmonary complications such as empyema and broncho-pleural fistula in 8.3 per cent for a combined incidence of pleuralpulmonary complications of 15.8 per cent.

Pleuropulmonary amebiasis occasionally is due to systemic invasion but is usually a direct extension of amoebic abscess such as in the case reported here. It is extremely doubtful whether primary infection of the lung occurs without antecedent bowel infection. Transphrenic immigration of amoebae to the lung via lymphatics has been mentioned as a possibility but is rare. A rupture of a liver abscess into the lung parenchyma may produce a bronchial fistula (30 per cent) such as occurred in this reported case, or pulmonary abscess (34 per cent) may follow.

In pleuropneumonic amebiasis, the clinical manifestations vary with extent and mode of infection. Pain is the most common single complaint, usually sharp, stabbing in the right lower chest or liver region frequently radiating to the shoulder; dyspnea may be present when the abscess is large; cough usually is unproductive but when large quantities of purulent material and chocolate sauce material appears in the sputum this is pathognomonic of hepatobronchial fistula. Other rather common manifestations are fever, anorexia, malaise, weakness, and weight loss. Jaundice is rare. Chest findings are characteristic of pleural effusion and roentgenographic examination may disclose a triangular shadow in both anterior-posterior lateral roentgenograms with its base toward the liver and apex extending toward the hilum of the lung (fig. 1).

The treatment of amoebic hepatic abscess and consequently its pleuropneumonic complications is entirely surgical whether conservative or radical therapy is employed. Early recognition of hepatitis and prevention of abscess formation or progression to pleuropneumonic involvement will result in a greatly reduced mortality. Emetine hydrochloride is specific for amoebic hepatic disease and usually is administered intramuscularly daily in 1 gr. (0.065 Gm.) doses for a total of 6 to 10 gr. Following the completion or during the course of emetine, the intestinal amebiasis should be treated with a suitable amebicidal drug such as carbarsone, diodoquin, etc., as outlined by Collins.[4] Failure to treat the intestinal infection adequately probably accounts for many recurrent abscesses.

Closed drainage by aspiration is the procedure of choice when evacuation of a liver abscess becomes necessary. Aspiration must always be preceded by preliminary administration of emetine hydrochloride for two to four days. Every attempt must be made to maintain sterility as secondary infection of the abscess results in a much higher mortality. Open drainage employed in 80 cases incurred a 22.1 per cent mortality in contrast to 3.6 per cent mortality in 83 cases treated by closed drainage in Ochsner's series.[1] Bockus,[5] however, does not favor aspirating liver abscesses for diagnosis because of the danger of soiling the peritoneum, pleura, or lung.

A suspected amoebic hepatic abscess should not be subjected to exploratory aspiration without cognizance of the possible dangers of 1. hemorrhage, and 2. extension of the infection. Pre-aspiration emetine therapy largely avoids these complications and the aspiration procedure should be carried out preferably in an operating room to assure absolute aseptic technic.

If open drainage becomes unavoidable when the amoebic abscess is secondarily infected, then two general types of surgical approaches are used: 1. transthoracic, and 2. transabdominal with either procedure completely avoiding contamination of the two virgin surfaces, pleural and peritoneal, by means of extraserous approach. The most popular method is that of Beck's two stage procedure.[6] The first stage consists of suturing the costophrenic pleural reflection and packing the wound with an irritative substance to stimulate the formation of adhesions. The second stage consists of later incising through to the abscess so the drainage is confined in the previously formed fistula.

Other complications of amoebic hepatic abscess are rupture into the peritoneal cavity (6 per cent), pericardial cavity perforation (2 per cent), and an even rarer complication of cerebral abscess which is almost invariably fatal.

The prognosis in pleuropulmonic amoebic involvement is poorest in the cases in which the hepatic abscess ruptures into the pleural cavity without subsequent adequate drainage, and best in those in which a bronchohepatic fistula develops with minimal pulmonary reaction. Incomplete evacuation of the liver abscess through the bronchus may result in empyema, a complication with 77.7 per cent mortality in the collected cases of Ochsner.[1] Liver abscess with extension into the lung incurs a 43 per cent mortality whereas in bronchohepatic fistula where drainage is usually adequate, the mortality of 10 per cent is much more favorable.

Summary

The most frequent complication of amoebic hepatic abscess is pleuropneumonic involvement. The diagnosis of this complication depends primarily on a high index of suspicion in patients with unexplained symptoms referable to the right side of the chest and diaphragm. A case of amoebic hepatic abscess with bronchohepatic fistula has been described in which there was rapid improvement with antiamoebic therapy and closed drainage.

References

1. Ochsner, A., and DeBakey, M.; Amoebic hepatitis and hepatic abscess; analysis of 181 cases with review of literature. Surgery 13:460 (March) and 612 (April), 1943.
2. Payne, A. M.: Amoebic dysentery in Eastern India. Lancet 1:206-209 (Feb. 17) 1945.
3. Ochsner, A., and DeBakey, M.: Pleuropulmonary complications of amebiasis; analysis of 153 collected and 15 personal cases. J. Thorac. Surg. 5:225-258 (Feb.) 1936.
4. Collins, E. N., and Bynum, F. L.: Amebiasis and indeterminate ulcerative colitis; combined therapy as applied to veterans from overseas. M. Clin. North America p. 408-418 (March) 1948.
5. Bockus, H. L. et al: Gastro-enterology, vol. 2 (Philadelphia: W. B. Saunders Company, 1944) p. 630-634.
6. Beck, C.: On diagnosis and treatment of abscess of lung. New York M. J. and M. Rec. 66:287, 1897.

THE VALUE OF VITAMIN B_{12} IN PERNICIOUS ANEMIA

Preliminary Report

DONALD W. BORTZ, M.D.
Department of General Medicine

SINCE the original work on vitamin B_{12} was reported in 1948, numerous articles have appeared confirming the effectiveness and potency of vitamin B_{12} in producing remissions in pernicious anemia. The original work[1] was done in the laboratories of the Merck Company, who generously supplied the material used in our cases. It was shown by Shorb[2] and West[3] that a factor, the LLD, could be found in liver extracts in direct proportion to the unit potency of the extracts used in pernicious anemia. As hypothesized by Rickes et al, 1 unit of vitamin B_{12} is equivalent to 1 USP unit of liver extract, and may produce equivalent hematopoietic response. This material has been isolated from whole liver and is believed to contain cobalt, phosphorus, and nitrogen. It is commercially obtained from the growth of Streptomyces griseus. It has been shown, too, that satisfactory responses may be expected to occur neurologically. Vitamin B_{12} is ineffective when given orally, yet when mixed with gastric juice passed through a Berkefeld filter, its effectiveness in preventing a megaloblastic arrest is complete.[4]

The present communication deals with the first 5 cases whom we now have under observation and treatment for pernicious anemia with vitamin B_{12}.

Case Reports

Case 1. A woman, aged 55, was seen initially on February 19, 1949, with a chief complaint of "something eating my blood." She first consulted her physician in 1940 because of paleness and weakness and was found to be anemic. Treatment by pills and injections of iron was ineffective. In 1944 a cholelithiasis was demonstrated, and prior to surgical removal of the gallbladder, the patient was given liver and iron injections. Inasmuch as diarrhea, nausea, and vomiting occurred following each liver injection, it was discontinued. Following the removal of the gallbladder, the patient felt improved for a year and a half, but again consulted a physician in December 1948 because of weakness and paleness. She was given four transfusions and referred to the Cleveland Clinic for study. On physical examination the significant findings consisted of a pale but not atrophic tongue. A definite generalized vitiligo was noted. She had no evidence of neurologic involvement of the spinal cord. Her laboratory data revealed a fractional test meal with an absence of any free hydrochloric acid and a total acidity of only eight units at the end of sixty minutes. Urinalysis, blood sugar, blood serology, bromsulfalein, and basal metabolic rate determinations were all negative. Her initial blood count and subsequent blood counts are shown in table 1. Sternal marrow aspiration revealed a magaloblastic bone marrow.

A test dose of liver extract during treatment with vitamin B_{12} produced the previously noted complaints of diarrhea, nausea, and vomiting. Four days after the institution of vitamin B_{12} therapy, the patient began to notice subjective improvement, which has persisted, and she now has the feeling of complete well being. She receives 10 micrograms of vitamin B_{12} every other week, two months following the institution of therapy.

Case 2. A woman, 62 years of age entered the Clinic because of a lack of appetite and inability to sleep. In addition, in the past year she had noted numbness and coldness of the

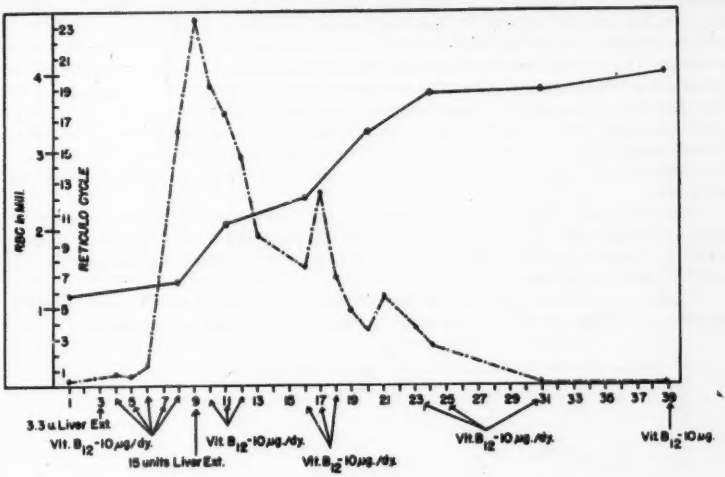

RBC in Mill.
RETICULO CYCLE
3.3 u. Liver Ext.
Vit. B_{12} - 10 µg/dy.
15 units Liver Ext.
Vit. B_{12} - 10 µg./dy.
Vit. B_{12} - 10 µg./dy.
Vit. B_{12} - 10 µg./dy.
Vit. B_{12} - 10 µg.

TABLE 1

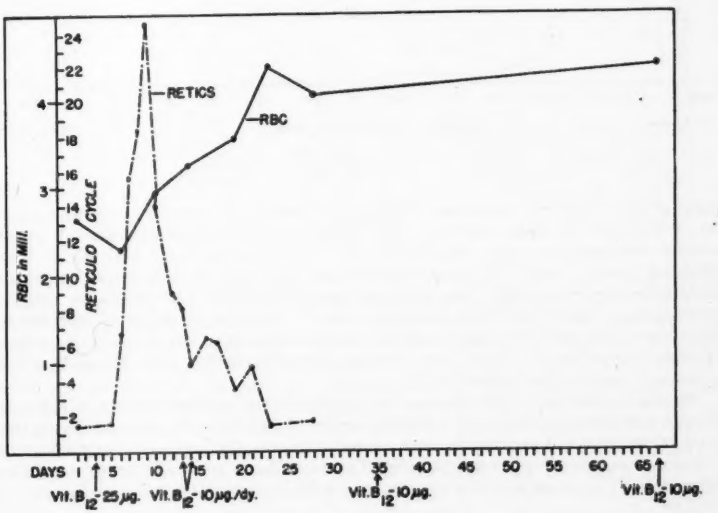


TABLE 2

lower extremities, associated with tingling and perspiration. Vague abdominal distress, nausea, bloating, and distention had been present for the past five years. A weight loss of nine pounds had occurred in the preceding seven months. For eight years she had received liver injections of unknown concentration, and developed swelling, redness, and tenderness at the site of the injection. For this reason no treatment had been received for eight months. On physical examination it was noted that her blood pressure was 170 systolic and 70 diastolic. The skin was sallow, and the tongue smooth and glossy. No spleen was felt, and the vibratory sense was intact. The urinalysis, blood urea, blood sugar, and cholesterol values were within normal limits. The serology was negative. The Ewald test meal revealed an absence of any free hydrochloric acid with a total acidity of only eight units. The bone marrow was megaloblastic.

Twelve days after the initial injection, all evidences of numbness and tingling had completely subsided. Her strength had returned to normal, and she was symptom free (table 2). Four months following initiation of treatment she was being adequately controlled with 10 micrograms every month.

Case 3. A woman, aged 52, presented herself because of rectal soreness of six years' duration, a "funny mouth" of fourteen months' duration, and a soreness of the mouth and

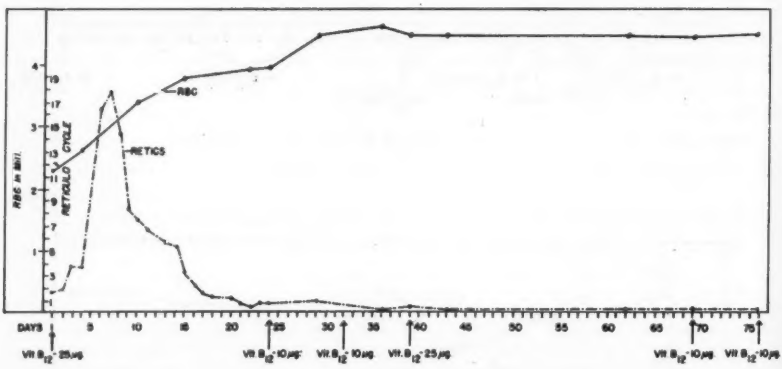


TABLE 3

tongue of sixteen months' duration. A diagnosis of pernicious anemia was made a number of years before and she stated that she had received liver extract of an unknown potency at irregular intervals since then, although a gastric analysis had never been done. A definite pallor was present, and the tongue was obviously atrophic. No spleen was palpable. Peripheral reflexes were normal. The vibratory sense was intact. The urinalysis, blood sugar, blood serology, and metabolism tests were normal. The Ewald test meal revealed no free hydrochloric acid with only eight units of total gastric acidity. An initial bone marrow was definitely megaloblastic, but it had become normoblastic five days following the initial injection of vitamin B_{12} (table 3).

Decided subjective improvement was noted within twenty-four hours following the first injection of vitamin B_{12}, and a definite feeling of well being five days following the institution of treatment. Two months later, the tongue was still red with the edges somewhat atrophic. However, upon 10 micrograms of vitamin B_{12} at weekly intervals, the tongue returned entirely to normal in four months, and adequate control is being maintained on this schedule.

Case 4. A man, aged 63, was initially seen at the Cleveland Clinic for a general check-up with relationship to beryllium poisoning. He was completely symptom-free with the exception of some manifestations of cardiac neurosis. His physical examination was entirely normal

at this time. The laboratory data revealed a normal urinalysis, blood sugar, and Wassermann and Kahn reactions. The blood count revealed 75 per cent hemoglobin with 4,230,000 red blood cells. One year later this patient returned because of extreme fatigue, anorexia, and loss in weight of twenty pounds in the past four months. Some diffuse generalized muscular aching had occurred recently. The physical examination was satisfactory with the exception of a clean but not atrophic tongue. There was no splenomegaly. The reflexes were all physiologic, but there was a decreased vibratory sense of the right leg, extending from the ankle to the mid right lower leg. At this time the Ewald test meal revealed the absence of any free hydrochloric acid with a total acidity of only eight units. The bone marrow was megaloblastic. Urinalysis and chest x-ray was normal. Electrocardiogram showed a first degree atrio-ventricular block. Vitamin B_{12} therapy was started, as noted in table 4, and one week following institution of treatment, the vibratory sense began to improve, as well as his appetite. Twelve days following treatment, the vibratory sense was completely intact, shortness of breath upon exertion had subsided, and the patient was gaining rapidly. He is being maintained on 10 micrograms at intervals of two weeks, adequate control having continued since ten weeks after institution of treatment.

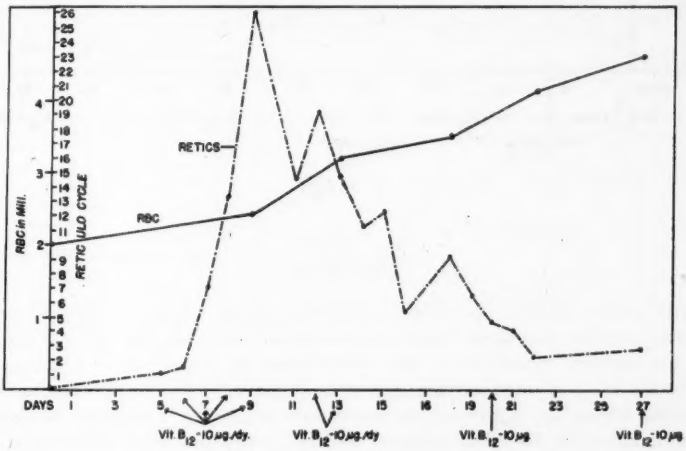


TABLE 4

Case 5. A 73-year-old woman was initially seen in the Department of Endocrinology because of a rapid heart and palpitation. Her physical examination revealed a pulse of 100, but no exophthalmus, lid lag, or tremor. The goiter was nodular and of an estimated weight of 80 Gm. Her tongue was smooth and atrophic. The reflexes of the knees and ankles were absent, and the vibratory sense was impaired in both knees and ankles. The chest x-ray, urinalysis, and blood sugar examinations were normal. The bone marrow was megaloblastic. The Ewald test meal revealed no free hydrochloric acid with a total acidity of only 3 units. The basal metabolic rate was plus 22, and a true hyperthyroidism was indicated when the basal metabolic rate remained high even following adequate control of the pernicious anemia with vitamin B_{12}. Ten mc. of I^{131} were accordingly given following the return of the blood picture to normal. Her glossitis had subsided by February 21, 1949, but slight impairment of the vibratory sense persisted until March 21, 1949 (table 5). The dosage of this patient is altered by the increased basal metabolic rate with adequate control of her hyperthyroidism, she is being maintained on 10 micrograms of vitamin B_{12} every other week over an observation period of three months.

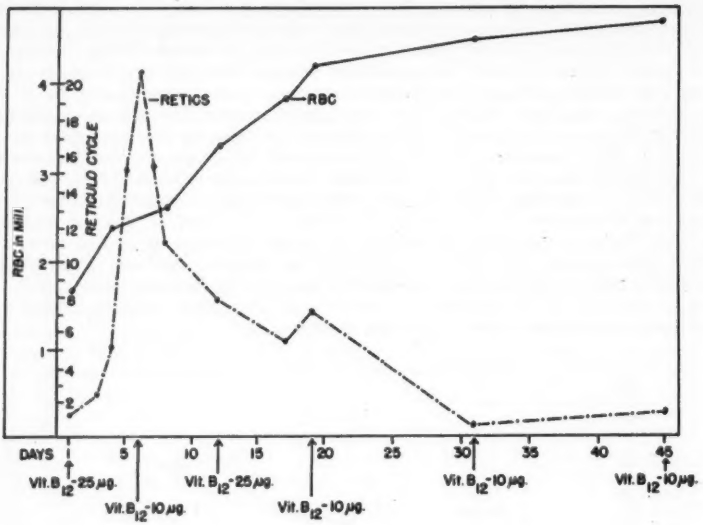


TABLE 15

Conclusion

The inconstancy of any dosage schedule which we have followed merely confirms the fact that there has been no accepted schedule for optimal response and maintained remission. If the observation is correct that a microgram of vitamin B_{12} is equivalent to a unit of liver extract 15 micrograms at monthly intervals should be sufficient for continued remission. Certainly bone marrow changes may be demonstrated within a very few hours following institution of vitamin B_{12} therapy. The height of the reticulocyte response is equivalent to that which one might expect under liver therapy. Interestingly enough, the patients all seem to develop a feeling of well being shortly after beginning treatment with vitamin B_{12}. Strength and vigor returned upon one occasion within twelve hours. The red blood count and hemoglobin return quickly to normal, but there apparently is a lag in the volume index in falling to normal limits. Leukopenia slowly resumes normal levels. An effort is now being made to maintain patients on 10 micrograms at two-week and four-week intervals. It is suspected that in due course of time, an ampule containing 15 micrograms will permit adequate control at monthly intervals. Vitamin B_{12} has also been effective in the treatment of nutritional macrocytic anemia, as well as non-tropical[5] and tropical sprue,[6] but has been ineffective in the treatment of the macrocytic anemia of pregnancy as reported by Day, Hall, and Pease.[7] Although vitamin B_{12} is the only substance yet isolated which apparently produces hematologic and neurologic remissions in patients with

pernicious anemia, similar to those which we have come to expect with liver extract, it must still be recognized that until vitamin B_{12} has been proven by the test of time, parenteral liver extract in proper doses is still the treatment of choice for pernicious anemia.

Addenda. Since the preparation of this paper 3 additional patients with pernicious anemia have been placed on vitamin B_{12} therapy. The one patient had severe pyramidal tract involvement which responded well to intensive vitamin B_{12} treatment. The second patient has failed hematologically to return entirely to normal, and the diagnosis of coexistent chronic liver disease is being entertained; and the third patient with coexistent carcinoma of the prostate is responding satisfactorily.

References

1. Rickes, E. L. et al.: Crystalline vitamin B_{12}. Science **107**:396-397 (April 16) 1948.
2. Shorb, M. S.: Activity of vitamin B_{12} for growth of lactobacillus lactis. Science **107**:397-398 (April 16) 1948.
3. West. R.: Activity of vitamin B_{12} in Addisonian pernicious anemia. Science 107: 398 (April 16) 1948.
4. Hall, B. E., Morgan, E. H., and Campbell, D. C.: Oral administration of vitamin B_{12} in pernicious anemia. I. Presence of intrinsic factor in Berkefeld-filtered pooled human gastric juice: preliminary report. Proc. Mayo Clin. **24**:99-107 (Feb. 16) 1949.
5. Spies, T. D., Stone, R. E., and Aramburu, T.: Observations on antianemic properties of vitamin B_{12}. South. M. J. **41**:522-523 (June) 1948.
6. Spies, T. D., et al: Observations hemopoietic response of persons with tropical sprue to vitamin B_{12}. South M. J. **41**:523-525 (June) 1948.
7. Day, L. A., Hall, B. E., and Pease, G. L.: Macrocytic anemia of pregnancy refractory to vitamin B_{12} therapy; response to treatment with folic acid: report of case. Proc. Mayo Clin. **24**:149-157 (March 30) 1949.

INTESTINAL OBSTRUCTION

Gallstone Impaction

JOSEPH C. ROOT, M.D.
Department of Roentgenology

ACUTE intestinal obstruction is a medical emergency requiring prompt diagnosis and treatment. Time is an important factor in this condition and without relief, ileus, with its vicious cycle, may develop. With the advent of the roentgen examination and its subsequent improvement in technic for visualization of the gastrointestinal tract, extensive strides have been made in the diagnosis of intestinal obstruction. This procedure may be employed, not only as a means of diagnosis, but also for localization of the site of the lesion and its possible cause. Having ascertained the approximate location, the surgeon may better plan his approach for alleviation of the condition.

There are, of course numerous causes for an acute obstruction, the most common comprising peritoneal adhesions from previous inflammatory disease or operation. Among other causes, in diminishing frequency, are neoplasm, intussusception, volvulus and impaction of gallstones. The latter is somewhat uncommon and found to be present in less than 2 per cent of all acute intestinal obstructions. History of previous biliary disease is suggestive but definite diagnosis and localization may be made in most instances by the roentgen examination.

Case Report

A 67 year old widow entered the Cleveland Clinic March 8, 1948, complaining of vomiting and inability to eat. The patient had been well until July 1947 when she suddenly contracted severe pain in the right upper abdomen and flank which seemed to travel downward toward the right hip and was accompanied by vomiting. This condition persisted for two days with additional symptoms of weakness and poor appetite.

In October 1947 she became jaundiced and large gallstones were discovered upon examination. Operation was attempted but the patient became unconscious on anaesthetic administration, whereupon surgery was postponed and she returned to her home.

No untoward symptoms presented themselves until about two weeks prior to her present admission when she again experienced nausea, loss of appetite and extreme weakness. Gripping transabdominal pain occurred prior to vomiting. The patient suffered from chronic constipation. She had recently emitted black vomitus.

Her personal history was essentially satisfactory except for having experienced malaria in childhood and jaundice at the age of 24.

Physical examination divulged extreme tenderness over the right hypochondrium, the right half of the epigastrium and the lumbar area. The muscles were splinted and the liver showed indications of enlargement. Some suggestion of a mass was evident in the epigastrium.

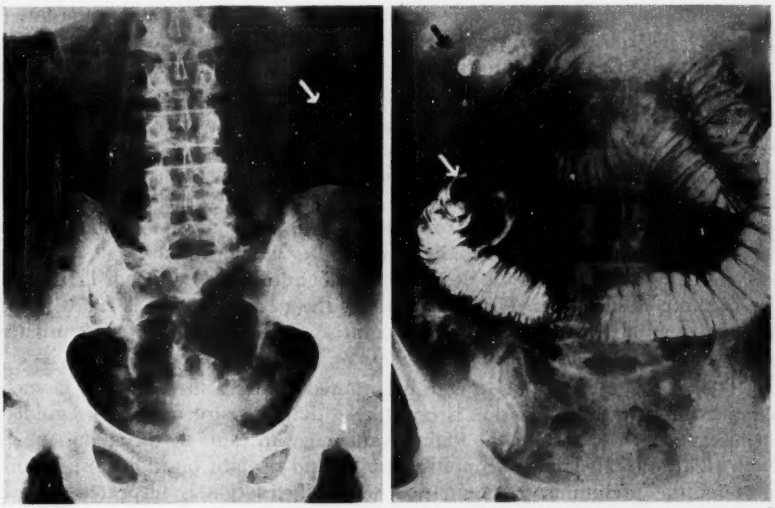
The roentgen examination disclosed a normal chest. A film taken for the kidneys, ureter and bladder revealed minimal hypertrophic changes of the lumbar vertebrae. A large, somewhat circular, faintly calcified shadow was present in the left upper quadrant. This shadow was suggestive of a "signet-ring" gallstone. No calcifications were found in the urinary tract.

Opaque shadows were not seen in a plain film of the gallbladder. The stomach and esophagus were normal with no organic lesion demonstrated in the former, although a considerable amount of fluid was present at the time of fluoroscopic examination. The duodenum was normal except for minimal dilatation and for this reason a six hour retention

film was ordered. In the roentgenograms of the stomach and duodenum there was suggestion of a small amount of gas in the hepatic radicles. The six hour retention film demonstrates obstruction in the distal portion of the jejunum with moderate dilatation proximal to that point. Just proximal to the site of obstruction is a rounded, nonopaque shadow. Barium is visualized in the hepatic radicles.

The operation, a transintestinal removal of impacted gallstone, was performed by Dr. George Crile, Jr. At a level of approximately two feet from the duodeno-jejunal junction, was a hard, oval stone measuring about 4 cm. by 6 cm. This was impacted and produced complete obstruction of the intestine. The duodenum and pyloric portion of the stomach were firmly attached to the liver in the region of the gallbladder and it was assumed that a spontaneous cholecystoduodenostomy had occurred. Further exploration of this area appeared inadvisable.

The patient made an uneventful recovery and left the hospital on the sixteenth postoperative day.



(a) (b)

FIG. 1. (a) Plain film of abdomen. Faintly visualized "signet-ring" shadow in left upper abdomen suggestive of gallstone; (b) obstruction of jejunum with dilatation proximal to site of obstruction. Large gallstone shown (white arrow). Black arrow designates barium in hepatic radicles.

Discussion

Obstruction of the intestine, partial or complete, may be due to any local pathologic condition which prevents the flow of intestinal contents. It may exist without ileus although the latter will ensue if the block is not relieved, and can exist without a mechanical obstruction; for that reason this term should not be considered synonymous with obstruction. Ileus, then, can be defined as a dilatation of the intestine, either a portion or its entirety, with excessive gas or fluid within the lumen. Disturbances of the physiology of the intestine contribute to, as well as result from ileus.

The small intestine has the inherent ability to cope with obstruction. Eventually, however, dilatation occurs due to fatigue of the musculature and an anoxemia of the muscle fibers from a disturbed blood supply. Compensation may be re-established at intervals by the intestine but the process frequently progresses into the terminal stage of tissue necrosis if the obstruction is not relieved by intubation or surgery.

The fluid contained in the dilated bowel is caused by ingested fluid as well as an increased secretion and diminished absorption. The small intestine performs both of these functions, secretion from the upper portion and absorption from the distal portion. With dilatation the actions are disturbed due to interference with the circulation from compression of the capillaries within the intestinal wall. The gas may result from swallowed air, diffusion of blood gasses into the lumen or the decompensation of intestinal contents, the latter probably the most important source. However, with the onset of dilatation a vicious cycle is set up with production of more fluid and gas which in turn increases the degree of dilatation.

The term paralytic or dynamic refers to an ileus in which there is no intrinsic obstructing cause within the intestine. Such a condition may result from peritonitis or even distant infection from the lungs or kidneys. Neurogenic disturbances such as spine injury may contribute to this condition. Vascular occlusion in mesenteric thrombosis is an important etiologic factor of a localized ileus which may rapidly progress to the terminal stage of tissue necrosis. In general, paralytic ileus follows much the same course as ileus from an intrinsic obstruction. The distention in the paralytic type is more likely to involve all of the intestinal tract in contrast to segmental dilatation usually observed with an early obstructive ileus.

The roentgen examination is of undisputed value in the diagnosis of such cases. Many times localization is possible so that the surgeon may be guided in his approach to the lesion. Plain roentgenogram films of the abdomen in both right and left lateral decubitus, supine and upright positions are important for the preliminary examination when obstruction is suspected. These roentgenograms should be made without prior cleansing preparation since a laxative may produce disastrous consequences and enemas tend to introduce confusing air or fluid shadows. A single film taken with the patient supine (fig. 1a) will frequently give evidence of the causative factor. When ileus has developed the roentgen examination shows a more or less set pattern regardless of the cause. This is characterized by the distended gas-filled loop or loops of intestine and the fluid levels which may be visualized in the decubitus and upright positions. Gas, as a rule, is not present in the normal small intestine although it may be seen at times in somewhat large quantity as with ureteral colic. In such instances, however, there is little or no distention of the lumen. Localization in the plain films depends upon the location and appearance of the gas-filled loops in the abdomen. The mucosal folds in the jejunum are rather high but tend to become smaller as the distal portion of the ileum is reached. The high folds are not easily obliterated when the bowel is distended so that cross striations or a "herring-bone" pattern in a high obstruction can be

visualized. A dilated distal ileum shows smooth walls and may be confused with the colon if the distention is pronounced. With caution a thin barium mixture may be given, either orally or through a Miller-Abbott tube for better localization of the site of obstruction (fig. 1b). By use of the barium the nature of the obstruction may be observed, whether caused by peritoneal adhesion, neoplasm or foreign body. No complications following administration of thin barium mixture have occurred and this procedure is employed even with existence of ileus. In such a case a small amount, approximately 20 to 30 cc. is injected through the Miller-Abbott tube and under fluoroscopic control. Survey films and additional fluoroscopic examinations are then made at appropriate intervals until adequate visualization of the intestine is obtained.

A NEW DIAGNOSTIC TEST FOR ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS*

JOHN R. HASERICK, M.D., and DONALD W. BORTZ, M.D.

Departments of Dermatology and General Medicine

(With the technical assistance of Miss Mary Stepien)

THE value of the bone marrow examination as a diagnostic aid in acute disseminated lupus erythematosus has been previously reported.[1] Subsequent experience has confirmed the worth of this procedure, but difficulties have been encountered in patients with hypoplastic marrows, and in patients who are considered too sick for even the relatively minor trauma of a sternal puncture. It therefore seems appropriate to report a new diagnostic method, utilizing only the plasma of the patient acutely ill with suspected lupus erythematosus, and the cellular bone marrow of normal persons.

As originally noted by Hargraves, Richmond and Morton,[2] the striking feature of the bone marrow in acute disseminated L.E. is the L.E. cell, usually a polymorphonuclear leukocyte which has engulfed a large homogenized smoky blue material. In addition, polymorphonuclear leukocytes are occasionally seen clustered around masses of bluish staining material, forming "rosettes." These two observations have been considered as essentially the same phenomenon, with the L.E. cell as the end result (fig. 1a and b).

In a preliminary paper,[3] we reported the induction of the L.E. cell and clumping of polymorphonuclear leukocytes in normal bone marrow preparations by the simple addition of plasma from patients with acute disseminated lupus erythematosus. The phenomenon so induced was indistinguishable from those noticed in L.E. bone marrow preparations. Follow-up studies have emphasized the consistency of this response. This procedure has proved its value as a diagnostic test and as an indicator of severity of infection.

Technic

Plasma from a suspected case of acute disseminated lupus erythematosus is prepared by centrifuging oxylated blood. One half cubic centimeter of this plasma is added to the heparinized bone marrow material, freshly aspirated from a normal person.

The heparinized bone marrow and the suspected L.E. plasma are placed in a Wintrobe hematocrit tube, filling the tube as full as possible. The tube is centrifuged at 1000 RPM for five minutes, which separates the cells into a clearly defined myeloid-erythroid layer. This layer is drawn off by a pipette and smeared by the two cover slip method. Wright's stain is used.

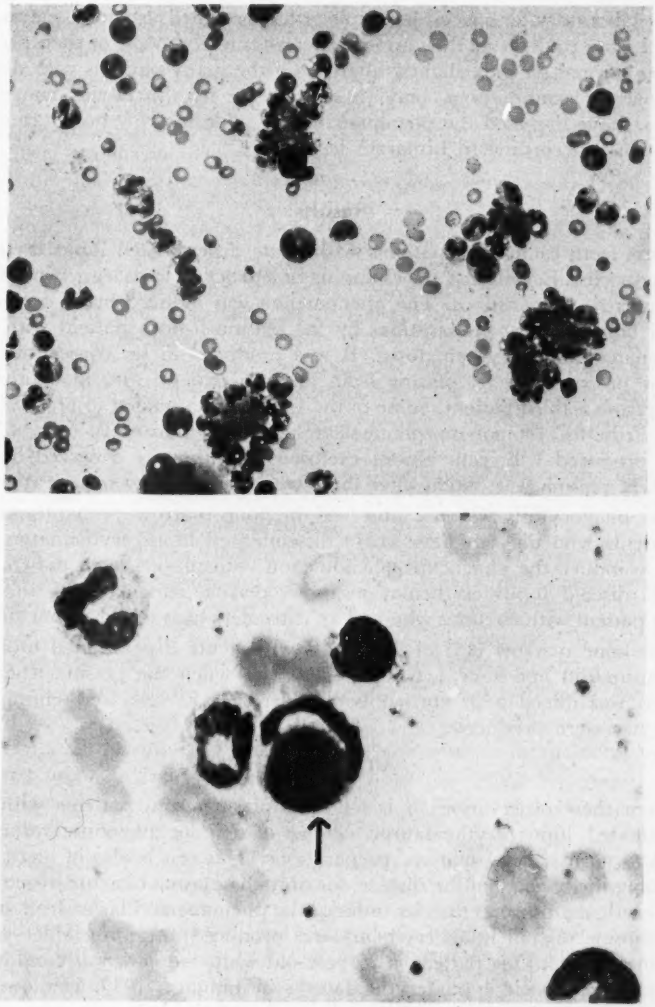
The entire procedure after mixing takes approximately one half hour.

In our studies three hematocrit tubes were used for each bone marrow

*Submitted March 29, 1949.

preparation. The first tube contained the normal heparinized bone marrow to which nothing had been added. The second tube contained bone marrow material plus the plasma of a patient suspected of having acute disseminated

(a)



(b)

FIG. 1. Phenomenon induced in a normal bone marrow preparation by L. E. plasma; (a) clumping of leukocytes; (b) the L. E. cell.

lupus erythematosus. The third tube contained the normal bone marrow preparation mixed with the plasma of a clear-cut case of acute disseminated lupus erythematosus. Comparisons were made of smears from each tube to determine the number of L.E. cells and the number of "rosettes" of polymorphonuclear leukocytes.

Our laboratory for special hematology has provided us with bone marrow material from patients as they appeared consecutively. Most of such preparations are normal, or only slightly altered. Of the many patients with diseased bone marrow examinations, only those with the highly cellular marrows of leukemia have impeded the phenomenon. All bone marrow preparations are concentrated according to Limarzi's technic.[4]

Results

Plasma from each of 14 patients with acute disseminated lupus erythematosus induced L.E. cells and the clumping of leukocytes in at least two different bone marrow preparations. The phenomenon was induced in 27 consecutive normal bone marrow preparations by the plasma from a patient with acute disseminated lupus erythematosus. It was produced in six consecutive bone marrow preparations by plasma from another patient, and in 4 others by plasma from a third patient. Some of the L.E. plasma tended to produce more of the "rosettes" of polymorphonuclear leukocytes than L.E. cells, whereas others produced L.E. cells almost exclusively. Both were observed in every case. L.E. plasma was potent after three weeks of ordinary refrigeration.

The phagocytosis was not observed in bone marrow preparations from 36 patients who did not have acute disseminated lupus erythematosus. We failed to induce the phagocytic phenomenon with plasma from patients with chronic discoid lupus erythematosus, scleroderma, rheumatoid arthritis, or from 1 patient with cirrhosis who had an extremely high total gamma globulin.

The bone marrow of 3 of 7 patients with acute disseminated lupus erythematosus did not show L.E. cells. However when the plasma from these patients was mixed with normal bone marrow L.E. cells and clumping of leukocytes were produced.

Comment

From these observations it is felt that plasma from patients with acute disseminated lupus erythematosus can be of definite diagnostic value when added to normal bone marrow preparations. This test is also of merit in determining the severity of the disease, for only the plasma of acute disseminated lupus erythematosus has thus far induced the phenomena. Plasma from patients with chronic discoid lupus erythematosus produced no appreciable variation from the normal. One patient, a 20-year-old white woman, was considered to have chronic discoid lupus erythematosus in January, 1949. Her own bone marrow preparation at that time did not reveal the L.E. cell. She returned in April, 1949, complaining of increased severity of joint pains, general malaise and high fever. Her plasma then induced large numbers of the L.E. cell in

normal bone marrow preparations. The sedimentation rate and the urine albumin were also greatly increased.

There was no correlation between the induction of L.E. cells and blood group incompatibilities.

The principal value of the test seems to be in clarifying obscure diagnostic problems. The hypothesis that the fraction of the plasma which induces the phagocytic phenomenon may be related to, or actually be, the etiologic agent in acute disseminated lupus erythematosus merits serious consideration. The ability to prevent this phenomenon through the alteration of the plasma by physical or chemical means, gives rise to interesting speculation: it is possible that a drug which would prevent the L.E. phenomenon would be of actual therapeutic value. Further studies are proceeding along these lines of investigation.

Summary

Plasma from 14 patients with acute disseminated lupus erythematosus induced the L.E. cell and clumping of polymorphonuclear leukocytes in the bone marrow of 48 normal patients.

Plasma from patients with chronic discoid lupus erythematosus, cirrhosis, scleroderma, or with rheumatoid arthritis failed to induce the phenomenon.

From these observations, we believe that the following conclusions may be drawn:

1. Plasma from patients with acute disseminated lupus erythematosus contains a substance which regularly induces the L.E. cell and clumping of leukocytes in normal marrows.
2. The L.E. cell observed in the bone marrow of patients with lupus erythematosus is therefore a secondary rather than a primary phenomenon.
3. The L.E. plasma—normal bone marrow preparation is a valuable diagnostic test in acute disseminated lupus erythematosus.
4. The plasma-marrow test is an indicator of severe systemic involvement in lupus erythematosus.
5. The L.E. plasma—normal bone marrow mixture merits consideration as a useful investigative tool.

References

1. Haserick, J. R., and Sundberg, R. D.: Bone marrow as diagnostic aid in acute disseminated lupus erythematosus; report on Hargraves' "L.E." cell. J. Invest. Dermat. **11**:209-213 (Sept.) 1948.
2. Hargraves, M. M., Richmond, H., and Morton, R. J.: Presentation of two bone marrow elements, "Tart" cell and "L.E." cell. Proc. Staff Meet. Mayo Clin. **23**:25-28 (Jan. 21) 1948.
3. Haserick, J. R., and Bortz, D. W.: Normal bone marrow inclusion phenomenon induced by lupus erythematosus plasma. J. Invest. Dermat. (In press)
4. Limarzi, L. R.: Evaluation of bone marrow concentration techniques. J. Lab. and Clin. Med. **32**:732-740 (June) 1947.

FATAL MAGNESIUM POISONING

*Following Magnesium Sulfate, Glycerin, and Water Enema in Primary Megacolon**

E. N. COLLINS, M.D., and P. W. RUSSELL, M.D.

Department of Gastroenterology

THE inclusion of magnesium sulfate in an enema in the presence of megacolon is extremely dangerous. Magnesium sulfate is unique in that it has both cathartic and anticonvulsant properties. When used to prevent convulsions it is given parenterally. When used as a cathartic, orally, in the presence of intestinal disease, the permeability of the intestinal membrane to magnesium may be increased and the effects on nerve function may predominate. The fact that the use of Epsom salt as a cathartic and in the treatment of biliary tract disease is usually harmless may lead to overlooking the possibility of its poisonous effects due to untoward absorption.

In the case reported death was due to magnesium poisoning resulting from absorption from an enema consisting of magnesium sulfate, glycerin, and water. An autopsy was performed.

Case Report

A boy, aged 4, was admitted to the Cleveland Clinic Hospital on July 2, 1948 with a history of abdominal enlargement and constipation present since birth. The patient never had had a spontaneous bowel movement. He had taken mineral oil orally each day since birth, but had no bowel function unless he was given pint enemas of mineral oil or soapsuds 1 to 4 times daily in addition. A left retroperitoneal ganglionectomy had been performed in 1946, and anal dilatation in 1947, without alteration of bowel habit. He had vomited about once a month.

Physical examination revealed an undersized boy of 4 years, weighing 25 pounds, with symmetrical abdominal enlargement. The abdominal wall was slightly atrophic and of doughy consistency. There was a tympanitic note to percussion in all quadrants, and no organs or masses were palpable. Hypoperistalsis was evident on auscultation. Digital rectal examination revealed a relaxed sphincter and a dilated rectum. The remainder of the physical examination did not reveal abnormalities.

Examination of the blood disclosed 11.5 Gm. of hemoglobin per 100 cc., 5,870,000 erythrocytes, and 11,000 leukocytes. The fasting blood sugar was 66 mg. per 100 cc. The urinalysis, blood Wassermann and Kahn tests were negative. A barium enema revealed filling of the colon to the splenic flexure, with a striking dilatation of the rectum and sigmoid. Further filling of the colon was unnecessary, as an extensive accumulation of gas demonstrated dilatation of the colon in all segments (fig. 1).

The diagnosis of primary megacolon was made. To determine the possible effect of lumbar sympathectomy in compensating for the neuromuscular dysfunction of the colon, a lumbar subarachnoid injection of 75 mg. of procaine was performed on July 8. Despite

---

*Dr. A. C. Corcoran, Research Division, assisted in the analysis of the factors involved in this case.

*Dr. Edith Farnsworth, Northwestern University School of Medicine, kindly performed the analysis which is gratefully acknowledged.

adequate level of anesthesia, spontaneous evacuation of the bowel did not occur. On July 9, at 2 p.m., a caudal epidural injection of procaine was given, which produced relaxation of the anal sphincter and increased peristalsis in the small bowel, but did not result in the passage of feces. After complete recovery from the anesthetic, at 3:30 p.m. an enema was administered. Prostigmine was to have been given to cause evacuation. The enema consisted of 2 ounces of a solution of magnesium sulfate containing 30 Gm. of the hydrated salt, 4 ounces of glycerin, and 6 ounces of water. Without expelling the enema, the child "fell asleep" about 4 p.m. At 5 p.m. he was found to be comatose, with complete flaccid paralysis

FIG. 1. Barium enema showing sigmoid and part of descending colon.

and absent pupillary reflexes. The respiratory rate was 8 per minute. This is important and characteristic. The pulse rate was 116 per minute. Cyanosis was absent. The patient was estimated to be in the second plane of third stage anesthesia. A rectal tube was immediately inserted. A subcutaneous injection of 0.4 cc. of prostigmine methylsulfate 1:4000 was given and caused release of about 1 pint of liquid fecal material. Following artificial respiration, oxygen, and 0.2 cc. of nikethamide subcutaneously the respiratory rate increased gradually to 16 per minute. The sequence of events indicated that the coma was related to the retained enema and probably to its magnesium content. Accordingly, at 6:30 p.m., 2 cc. of a 10 per cent solution of calcium gluconate was injected into the jugular vein, and an equal dose was

injected intramuscularly. Shortly thereafter, a slight increase in the respiratory rate was noted, but the neurological picture was unchanged. Despite continued supportive measures, including aspiration of additional fecal material, injections of 0.3 cc. of nikethamide, and 0.5 cc. of caffeine with sodium benzoate, the patient's condition remained the same until he died in respiratory paralysis at 10:30 p.m.

Postmortem examination showed the peritoneal cavity to be free of fluid and adhesions. The colon was hypertrophied, elongated, and grossly dilated, measuring 10 cm. in diameter. No perforations or stercoral ulcerations were found. There was a considerable quantity of fecal material in the left colon, but the small intestines were empty. A Meckel's diverticulum was encountered. There was no evidence of intestinal obstruction. Microscopic examination of the colon revealed thin mucosa infiltrated with leukocytes, an increased amount of submucosal connective tissue, and thickening of the muscular coats and serosa. Other significant microscopic findings included severe cerebral congestion with slight edema, congestion of the liver, lungs, and spleen, edema of the myocardium, and vacuolization of the adrenal cortex. A pathologic diagnosis of primary megacolon was made by Dr. John B. Hazard. Inasmuch as the gross and microscopic examination failed to reveal the cause of death, a specimen of heart blood was analyzed for magnesium.*

The serum magnesium at autopsy was 30 mg. per 100 cc. (25 mEq per liter), and the serum calcium was 20.8 mg. per 100 cc.

Discussion

It is known that progressive increase in the serum magnesium level above the normal of 2.4 mg. per 100 cc. results in nervous depression. In the cat these changes are apparently due to blocked neuromuscular transmission which affects different systems as the magnesium level rises;[1,2] tendon reflexes disappear at 6-14 mEq per liter, coma occurs at about 14.2 mEq per liter, natural respiration disappears at 15-20 mEq per liter, and corneal reflexes at 30-35 mEq per liter. All parts of the cardiac conduction system are also affected, S-A and A-V block occurring above a level of 15 mEq per liter. Cardiac arrest never precedes respiratory arrest, and usually occurs at levels of 27-44 mEq per liter. It may be concluded, therefore, that death in this case was due to respiratory paralysis.

Of 10 cases included in separate reports by Fraser[3] in 1909 and Boos[4] in 1910, only 2 presented the symptoms of coma and flaccid paralysis which constitute the known effects of magnesium poisoning; others manifested shock, syncope, or "intestinal intoxication" due to the local effects of overdosage. Maxwell[5] in 1929 reported the rapid onset of coma, paralysis, and death due to peritoneal absorption of an enema containing 15 Gm. of magnesium sulfate. This had been given to a patient whose sigmoid colon had been inadvertently transected. Byron[6] in 1939 reported 5 cases of fatal poisoning following oral administration of Epsom salt to children with helminthiasis. An unpublished fatality following rapid intravenous injection of 7.5 Gm. of magnesium sulfate is cited by Winkler, et al.[7] in 1942. In none of these 9 typical cases of magnesium poisoning, all of which were fatal, were there confirmatory laboratory data.

Fawcett and Gens[8] in 1943 reported 2 cases of magnesium poisoning following enemas, one presumptive, and the other the *first proved case*. One patient, a 2 year old boy, had an imperforate anus which had been treated with colos-

tomy followed by an abdominoperineal plastic operation. Two months postoperatively, an enema containing magnesium immediately resulted in flaccid paralysis, coma, and absent pupillary reflexes. Respiratory failure occurred a few hours later, and autopsy failed to reveal the cause of death. A 23 year old woman with ureteral calculus was given prostigmine and an enema containing 28 Gm. of magnesium sulfate. One hour later, she was found to be in a coma, with flaccid paralysis and sluggish pupils. One gram of calcium gluconate intravenously gave prompt improvement. Three hours later, the serum magnesium was 20.8 mg. per 100 cc., and the serum calcium 9.9 mg. per 100 cc. An additional 1 Gm. of calcium gluconate intravenously resulted in complete recovery of consciousness, at which time the serum magnesium was 15.4 mg. per 100 cc., and the serum calcium 11.2 mg. per 100 cc. Of the 11 reported typical cases of magnesium poisoning, this was the only one to recover.

A fact not sufficiently appreciated is that the gastrointestinal membrane is by no means impermeable to the salts of magnesium. Hirschfelder[9] found that 40 per cent of an oral dose of magnesium sulfate was absorbed within twenty-four hours; he emphasized that the rapid urinary excretion of magnesium which normally prevails prevented a significant rise in serum concentration, and that when excretion was depressed, as in nephritis, dangerous serum magnesium levels could be obtained with an ordinary oral dose. Van Liere[10] demonstrated in dogs 14 per cent absorption of magnesium in ninety minutes from ileal loops filled with 3.25 per cent anhydrous magnesium sulfate.

Winkler, et al. calculated the fraction of the body water in which magnesium is distributed following a known retention of an injection of magnesium sulfate. Assuming from their data that the increased magnesium concentration prevailed in 30 per cent of the body weight of our patient, it appears that this child absorbed at least 34 per cent of the 3000 mg. of magnesium present in the enema. The reason for this absorption was not evident from the postmortem examination. Other cases of primary megacolon are known to have received such enemas without untoward results; Bonar[11] repeatedly administered enemas containing 56 Gm. of magnesium sulfate to a 4 year old child with megacolon and obtained excellent evacuations of the bowel.

The only effective antidote in magnesium poisoning is parenteral administration of calcium ion. The proper dosage of calcium needed to antagonize a given magnesium excess has not been calculated. The response to calcium obtained in experimental animals appears immediately so that the dosage can best be judged by clinical improvement. This was also apparent in the case presented by Fawcett and Gens, who injected 90 mg. of calcium ion. The dose of 36 mg. of calcium ion used in our case would seem sufficient by comparing body weights, yet no clinical improvement was noted.

Curiously, the final serum calcium level was 20.8 mg. per 100 cc. This hypercalcemia is difficult to explain. Assuming a plasma volume of 570 cc., the total increase in serum calcium was about 57 mg., of which 36 mg. were injected, leaving an excess of at least 21 mg. of calcium in the serum. This might be regarded as a protective response of the body to hypermagnesemia.

We have not found this effect to be mentioned in the literature. That this hypercalcemia might also have blocked neuromuscular transmission seems unlikely, as higher levels of serum calcium are needed for such a depression to occur. We are, therefore, led to assume that the lack of response to calcium in this case was due not to under-dosage but to delay in its administration.

Summary

1. Fatal magnesium poisoning resulted from the absorption from an enema in a patient with primary megacolon.

2. The clinical signs of flaccid paralysis, slow respiratory rate, coma, and absent pupillary reflexes developing rapidly after the administration of magnesium sulfate must be promptly recognized if calcium therapy is to be beneficial.

3. The use of magnesium sulfate enemas is contraindicated in children with primary megacolon.

References

1. Hoff, H. E., Smith, P. K., and Winkler, A. W.: Effects of magnesium on nervous system in relation to its concentration in serum. Am. J. Physiol. **130**:292-297 (Aug.) 1940.
2. Smith, P. K., Winkler, A. W., and Hoff, H. E.: Electrocardiographic changes and concentration of magnesium in serum following intravenous injection of magnesium salts. Am. J. Physiol. **126**:720-730 (July) 1939.
3. Fraser, C.: Epsom salts as a poison: with a record of a case of unusual symptoms due to this drug. Lancet **1**:1174-1176, 1909.
4. Boos, W. F.: Magnesium poisoning. J.A.M.A. **55**:2037-2042 (Dec. 10) 1910.
5. Maxwell, W. W.: Traumatic perforation of uterus with severance of rectum; report of a case. Am. J. Obst. and Gynec. **17**:96-102 (Jan.) 1929.
6. Byron, F. E.: Fatal results following administration of magnesium sulfate. J. Malaya Br., Brit. M. A. **3**:100-101 (June) 1939.
7. Winkler, A. W., Smith, P. K., and Hoff, H. E.: Intravenous magnesium sulfate in treatments of nephritic convulsions in adults. J. Clin. Investigation **21**:207-216 (March) 1942.
8. Fawcett, D. W., and Gens, J. P.: Magnesium poisoning following enema of epsom salt solution. J.A.M.A. **123**:1028-1029 (Dec. 18) 1943.
9. Hirschfelder, A. D.: Clinical manifestations of high and low plasma magnesium; dangers of epsom salt purgation in nephritis. J.A.M.A. **102**:1138-1141 (April 7) 1934.
10. Van Liere, E. J., Northrup, D. W., Stickney, J. C., and Richards, R. E.: Effect of anemia anoxia on absorption of isotonic magnesium sulfate from small intestine. Proc. Soc. Exper. Biol. and Med. **64**:62-64 (Jan.) 1947.
11. Bonar, B. E.: Pelvirectal acholasia (Hirschsprung's disease); temporary medical management by rectal administration of magnesium sulfate. Am. J. Dis. Child. **48**:123-129 (July) 1934.

DIABETES

On March 17, 1949, the Frank E. Bunts Educational Institute presented a continuation course on Diabetes. There follow abstracts of the proceedings of this course.

THE PHYSIOLOGY OF INSULIN

E. Perry McCullagh, M.D.

Insulin comes from the islets of Langerhans, which are groups of about 30 cells weighing 1/120 of the weight of the pancreas. These cells are of several types; the alpha and beta cells are granulated, suggesting secreting power. The fact that insulin arises in the islet cells is supported by the fact that it is present when enzyme tissue is degenerated; moreover, it is present in adenomata or carcinomata of islet tissue. Its production is influenced either by pituitary extracts or alloxan, the effects of which are shown in microscopic changes of the islet cells, especially the beta cells.

Insulin, first produced in extracts by Banting and his co-workers in 1922, was crystallized by Abel in 1926. It is an interesting fact that it contains zinc. The hormone is a polypeptide of approximately the molecular weight of egg albumen. One of the most potent factors regulating insulin production is the amount of glucose reaching the pancreas in arterial blood.

Some of the important functions of insulin may be listed as follows:

1. It regulates blood glucose levels.
2. It effects the storage of glycogen in liver and muscles.
3. It influences utilization of sugar by the tissues.
4. It increases fixation of amino acids in tissues for production of protein.
5. It has indirect action on hepatic ketogenesis and consequently on blood ketones and fats.

Of physiologic importance is the fact that insulin normally flows directly to the liver.

The chief effect of blood glucose is by virtue of affecting glucose deposited. There is also good evidence that insulin prevents protein breakdown (productive of more sugar) within the liver. In this and in similar ways insulin effects nitrogen excretion.

In the absence of insulin there is a rise in the level of blood glucose, amino acids, urea, creatine and creatinine; also great shifts in blood electrolytes including sodium and potassium. Phosphorus is intimately affected since phosphorus is closely connected with the transfer of glucose from blood to tissues and in the preparation of glucose for immediate oxidation. When a fall of blood potassium occurs as a result of insulin withdrawal, myocardial changes occur which are shown in the electrocardiogram as a long Q-T interval with broad T waves, and in some cases prominent U waves.

It will become increasingly important to learn ways of measuring the amount of insulin in the blood. Current methods under examination include the measurement of transfer of radioactive phosphorus in an exchange between free phosphorus and that found in phospho-creatin in a muscle mixture treated with insulin. Another method is based on the hypersensitivity to insulin found in an hypophysectomized, adrenalectomized animal, or a method in which insulin is tested in an animal which is hypophysectomized, adrenal-medullectomized and made alloxan diabetic.

The recent work of the Coris may point to the mode of action of insulin. According to this theory, the enzyme hexokinase (with which adenosine triphosphate converts glucose into glucose 6 phosphate which can be metabolized) is inhibited by anterior pituitary or by adrenal extract. This inhibition is antagonized by insulin. Unfortunately as yet this reaction cannot be translated freely into clinical medicine.

THE DIAGNOSIS OF DIABETES

R. W. Schneider, M.D.

In severe cases the diagnosis of diabetes is simple, being recognized by polydipsia, polyuria, and weight loss and confirmed by finding glycosuria and hyperglycemia. In early or mild cases, symptoms are always absent. Glycosuria is often the only early sign and may appear so intermittently that diabetes may be too quickly eliminated when the urinalysis is negative. A specimen should be obtained one to two hours after a heavy meal since the fasting specimen in mild cases is apt to be negative. It has been estimated that about 5 per cent of cases have no glycosuria. Recognition of these cases depends entirely upon the presence of an elevated blood sugar. This includes individuals with "high renal thresholds" as well as those with early impaired carbohydrate tolerance.

In a few borderline cases blood sugar levels taken two or two and one half hours after a hearty meal may be abnormal, when fasting or four hour tests are normal. Duncan mentions a patient with a normal fasting blood sugar who was seen a few months later in coma with a blood sugar of 1260 mg. per cent.

Glucose tolerance tests may need to be employed in borderline cases and extreme care exercised in their proper interpretation. Occasionally, the diagnosis will best be deferred until more complete evidence can be obtained. The glucose tolerance test should be reserved for the mild cases which cannot be properly recognized without it, and to exclude the suspicion that diabetes is present when it does not exist. All too frequently, glucose tolerance tests are obtained on patients already known to have glycosuria and hyperglycemia. In such instances, the patient has been subjected to additional expense and inconvenience not to mention the possibility of some harm, and the physician emerges with no more precise information than he already possessed.

Sugar in the urine is presumptive evidence of diabetes. Approximately 90 per cent of cases are recognized in this way. The separation of diabetes from renal glycosuria must depend upon random blood sugar determination and, if necessary, a glucose tolerance test. Separation from other causes of glycosuria must also be considered. Temporary glycosurias may appear during the course of infection or secondary to thyroid, adrenal, liver and pancreatic disorders. Others follow brain injury,encephalography, emotional crises, or after the administration of drugs. False positive results occur in other melliturias such as from levulose, pentose or fructose as well as in alkaptonuria. The confirmation of the diagnosis of diabetes by the determination of an elevated blood sugar accompanying glycosuria will avoid such serious errors as inducing insulin shock in individuals with renal glycosuria or in depriving patients from securing life insurance at normal premiums when diabetes does not exist.

When glycosuria has been observed, the urine must also be examined promptly for acetone since its presence is a matter of great and immediate therapeutic significance.

The interpretation of borderline blood sugar levels is difficult due to lack of agreement about normal and abnormal values. Interpretation is further confused because of technical difficulties in methods.

We regard blood sugar levels of 120 mg. per cent or above when fasting or two and a half hours after food as being abnormal, but permit levels of 200 mg. per cent one-half to one hour after eating. Most insurance companies have regarded levels over 120 fasting as being abnormal, but vary in accepting levels between 160 and 225 as the upper limit one hour after food. When more widespread acceptance of one method of blood sugar determination has been obtained there will undoubtedly be uniformity of opinion regarding the normal limits of blood sugar levels.

In the use of the glucose tolerance test for the diagnosis of diabetes, there is no uniformity of opinion as to the method to be employed or its proper interpretation. We

have used the 100 Gm. single dose, oral glucose tolerance test routinely except in children in whom the amount has been reduced. Blood and urine samples are collected fasting and at one-half, one, two, three, and four hour periods following administration of glucose. We regard the test as being normal when the blood sugar has returned to 120 or less by the end of two and one-half hours. We regard the peak of the curve as the least single important diagnostic feature and place greater emphasis upon the speed of its return, viewing a lag up to three or four hours as important.

In the interpretation of abnormal glucose tolerance tests the effects of obesity, age, exercise, gastrointestinal absorption, disturbances within the pituitary, thyroid and adrenal as well as the liver, are the more important factors. In addition, the diet preceding the performance of the glucose tolerance test has a bearing upon its results. It is the effect of the previous diet upon the result of the test which is most likely to be overlooked. Normal persons who are starved or fed diets low in carbohydrates will display diabetic types of glucose tolerance curves. This factor can be eliminated by the administration of 250 to 300 Gm. of carbohydrate for three or four days before performing the test.

RECENT DEVELOPMENTS IN EXPERIMENTAL DIABETES

*Arnold Lazarow, M.D.**

Diabetes, a disease which is characterized by hyperglycemia and impaired glucose metabolism, has been produced in experimental animals by a wide variety of procedures. These include total or subtotal surgical removal of the pancreas, the injection of massive amounts of anterior pituitary or adrenal cortical hormones, and the administration of alloxan. In the intact animal there is an antagonism between the pancreas on the one hand and the pituitary and adrenal cortex on the other. Although metabolism is normal when all of these glands are present and functioning, an imbalance between the pancreas on one hand and either the pituitary or adrenal cortex on the other produces diabetes. Such an endocrine imbalance is produced by the removal of the pancreas or by the injection of excessive amounts of the anterior pituitary hormone. Although the injection of A.P.E. produces its initial effect by action on the liver, the long continued administration of anterior pituitary hormone produces a secondary degeneration in the beta cells of the pancreas and thereby produces a permanent or secondary pancreatic diabetes.

The discovery that alloxan produces diabetes in experimental animals (Dunn, Sheehan and McLetchie, Lancet 1:484, 1943) has stimulated a great deal of work on the etiology of diabetes. It has been shown that glutathione (Lazarow, Proc. Soc. Exper. Biol. and Med. 61:441, 1946) plays an important role in determining the susceptibility of rats to alloxan diabetes. When the glutathione content of the body is increased, by the prior injection of this sulfhydryl compound, rats are completely protected against a diabetogenic dose of alloxan; by contrast when the glutathione stores in the body are depleted by the injection of ascorbic acid, rats become more susceptible to alloxan.

Alloxan reacts with the sulfhydryl group of glutathione and with sulfhydryl groups of essential enzymes. It is suggested that the diabetogenic action of alloxan may be due to enzyme inactivation occurring as a consequence of sulfhydryl enzyme inactivation. Although alloxan selectively destroys the beta cells in the pancreas, it is also capable of destroying many other cells. Perhaps the specialization of the beta cells for the synthesis of insulin may predispose these cells to alloxan by lowering the beta cell gluta-

thione content. Cysteine, a sulfhydryl amino acid, is a precursor of both insulin and glutathione. (Twelve per cent of the amino acids of insulin are cysteine.) It has been calculated that if all of the cysteine contained in the glutathione of the beta cells of man were available for insulin synthesis, less than 20 units of insulin would be formed. This is but a fraction of the daily insulin requirement of man. Since the glutathione in the various cells of the body is not in rapid equilibrium the specialization of the beta cells for the production of insulin may result in a localized depletion of cysteine and glutathione and thereby may render these cells more susceptible to alloxan.

It is further suggested that the degenerative changes observed in the beta cells of the pancreas following subtotal pancreatectomy or following anterior pituitary hormone or massive glucose injection may in part be due to a localized depletion of the beta cell glutathione occurring as a consequence of an increased rate of insulin synthesis. Thus any factor which increases the rate at which insulin is synthesized by the beta cells would thereby tend to deplete beta cells cysteine and glutathione and thereby make these cells more susceptible to the action of toxic or metabolic factors which may normally appear within the human body.

*By invitation. Dept. of Anatomy, Western Reserve University.

SELECTION OF DIET

R. W. Schneider, M.D.

The optimum diet for the diabetic is that which will keep him well and strong, at the same time not permitting his weight to rise or fall far from ideal. It should be palatable and satisfying. Diets high in carbohydrate and low in fat or the reverse are not generally palatable. Men generally like diets higher in meat and are often not satisfied until 90 Gm. of protein per day is permitted.

The diet must also supply correct caloric requirements of the individual. It must be properly balanced with carbohydrate, protein, fat and total calories and should also meet the long-time requirements in vitamins and minerals. A gain or loss in weight will determine how correctly such requirements are being satisfied.

The selection of the diet best suited for the individual patient is the first problem which must be settled by the physician. One fundamental principal has been well established, namely, the avoidance of over-feeding. Prolonged over-nutrition often leads to fatty liver and this may increase the susceptibility to infection and coma. Certainly, diabetes is one penalty of obesity and the mortality rate in diabetes beyond 45 increases with the degree of excessive weight. Furthermore, Newburgh has shown that glucose tolerance tests may be returned to normal in more than three-fourths of those adult obese hyperglycemic patients who undergo adequate weight reduction.

It matters little what means of measurement of food is adopted: scales are best in the end but household measures in cups and spoons will serve when scales are not available. Accurate weighing of the food will repay the patient, however, by enabling him to estimate more accurately food quantities when he is without means of more accurate measurement.

In selecting the diet for the obese patient, the principle consideration is the total caloric intake. We commonly employ a diet supplying 100 Gm. carbohydrate, 62 Gm. protein and 50 Gm. fat, allowing a total intake of 1098 calories per day. We have employed this diet simply because it can be applied in the majority of obese subjects. The caloric intake may be increased or decreased in these obese individuals depending upon their customary activity.

Larger caloric prescription must be arranged for those with normal or subnormal

weights. The variations introduced by age, sex, height, basal metabolic rate and level of daily activity must be considered. The best ultimate guides are the general health in terms of weight and strength, and in children, growth. Periodic adjustment to higher or lower diets will frequently depend upon progress. Larger diets of necessity must be employed in children, manual laborers, and malnourished subjects.

General bodily structure may modify the prescribed caloric intake at times. A helpful rule is to allow 10 per cent additional weight for large-framed individuals and to substract 10 per cent for those of light frame.

Additional increments of food to allow for occupation may be permitted as follows: 10 per cent additional for people at room rest, 15 per cent for light work, 20 per cent for average work, 30 per cent for heavy work, and for growing children and manual laborers 40 to 50 per cent.

In general, we tend to maintain carbohydrate intake between 100 to 250 Gm. per day. We allow sufficient fat to keep the diet palatable and yet not overloaded. In our basic diet, the daily intake permits three servings of fruit, one egg, 500 Gm. milk, 15 Gm. butter, 100 Gm. of cereal or one slice of bread (15 Gm. carbohydrate and 3 Gm. protein).

As the diet is raised in bread or its equivalent, butter is also increased in increments of 10 Gm. Fat intake generally ranges from 50 to 150 Gm. per day, seldom higher. Protein is raised from 90 to 120 Gm. in manual laborers and in patients with liver disease or hyperthyroidism. In the past few years, we have also advocated 120 to 140 Gm. of protein per day in patients with diabetic retinopathy in an attempt to combat the hypoalbuminemia common to the majority of them. Occasionally advanced renal insufficiency seems to contraindicate its use, but seldom have we seen increasing azotemia following the addition of high protein feedings in such cases.

Our usual practice has been to divide the total quantity of food for the day into three equal parts, but many clinicians advocate supplementary feedings between meals and at bedtime in order to distribute the metabolic load more evenly over a greater number of hours. When protamine-zinc insulin is used, bedtime feedings are especially valuable. For individuals who do not require insulin, we distribute the available glucose into three meals permitting 25 per cent of the total for breakfast, 35 per cent for lunch and 40 per cent for the evening meal. When protamine-zinc insulin is used, the available glucose is distributed into four feedings, 20 per cent being given for breakfast, 30 per cent for lunch, 40 per cent for dinner, and 10 per cent at bedtime. We employ globin insulin infrequently, but when it is used the distribution is changed to 20 per cent for breakfast, 40 per cent for lunch, 10 per cent at the three o'clock feeding in the afternoon, and 30 per cent with the evening meal.

CALCULATING AND PLANNING DIABETIC DIETS

Marjorie R. Curry, B.S.

Good sources of food analyses are:

1. Food and Beverage Analyses by Milton Bridges.
2. Food Values of Portions Most Commonly Used by Bowes and Church.
3. Fundamentals of Nutrition by Mary Schwartz Rose.
4. Various Gov't. Bulletins from the Dept. of Agriculture for example: Miscellaneous Publication No. 572.

We build all diabetic diets on a basic meal plan. The total basic diet contains carbo-

hydrate—100 Gm., protein—64 Gm. and fat—50 Gm. to a total of 1106 calories. The diet contains for breakfast:

	carb.	*prot.*	*fat*
1 serving of fruit	10		
1 egg (soft-cooked or poached)		6	6
1 slice of bread (Preferably whole wheat)	15	3	
½ square of butter			4.2
½ glassful whole milk	5	3	4
for luncheon:			
3 ounces of cooked lean meat or an equal substitute		18	7.5
1 cupful cooked 5% vegetable	10	2	
1 cupful raw 5% vegetable	5	1	
½ square of butter			4.2
1 glassful of milk	10	7	8
for dinner:			
3 ounces of cooked lean meat		18	7.5
1 cupful cooked 5% vegetable	10	2	
½ cupful 10% vegetable	10	1	
½ square of butter			4.2
½ glassful milk	5	3	4

This diet provides the essential foodstuffs for protective nourishment, that is enough calories for maintenance, adequate protein containing essential amino acids, carbohydrate and fat to make up the caloric requirements, adequate bulk, vitamins, minerals, and certain fatty acids.

As the diet prescription is increased, additions of bread, cereals, cream, and other foodstuffs are made. For example the addition of one slice or 30 Gm. of bread adds 15 Gm. of carbohydrate (50 per cent of bread is carbohydrate) and 3 Gm. of protein bringing the total carbohydrate to 115, protein to 65, leaving the fat at 50, and yielding 1170 calories.

If the prescription of C 130, P 68 to 1800 calories is given, we calculate the fat content to 112 Gm. Our calculation then would add two slices of bread to the basic diet and for 62 added Gm. of fat, we might change the milk allowed at breakfast and dinner to 20 per cent cream adding 32 Gm. of the fat. The remainder might be added as butter (an additional 35 Gm. or 3½ squares) yielding 29.6 Gm. of fat.

This diet is given in just three meals daily. The type of insulin and its action also affects our meal planning scheme.

After the diet is arranged to fit the medical prescription, the personal equation enters the picture. The patient's food likes and dislikes must be accounted for as well as his ability to comprehend a diet instruction and his ability to purchase and prepare these foods. All diet instructions are given individually. When a language problem exists, we usually request the aid of one of the family as interpreter. For husbands, we frequently ask the wife to sit in on the instruction as she does the actual meal preparation.

Our first instruction to the patient is usually given in household measures unless specifically ordered as a weighed instruction. The average patient is familiar with cupfuls and glassfuls while gram weights are altogether foreign. As the patient learns the diet and becomes adjusted to a diabetic routine, we encourage him to buy gram scales and weigh his food.

For measuring, the term cupful always means an eight ounce measuring cup. A

glassful is six and one-half ounces. These measures work well with two exceptions, bread and meat. For these we use ruler measurements suggesting that they cut models for their use at home or as in many cases, where household scales are available, the patient weighs his bread and meat while measuring other foods. In all instructions, however, are discouraged because they are difficult to prepare accurately.

Each patient has definite food preferences so lists of fruits, vegetables, and meats permit him to select those which he prefers. The substitution list may be used to convert bread to potato or milk to meat and fruit or to alter the general outline so that he will not become tired of certain foods. In the case of foreign patients, we attempt to teach them how to fit their native dishes to their prescription. Complicated mixtures, however, are discouraged because they are difficult to prepare accurately.

During the actual instruction, major points of food preparation are emphasized. Fruits should be canned without sugar or fresh fruit in season. Meats should be either broiled, roasted, or stewed. Fat and bone should be trimmed from the meat before measuring because our calculations are on cooked lean meat (edible portion). Fat is one of the important factors of a low caloric diet. All fats (margarine, food oils, cooking fats, and bacon drippings) are permitted on our diets, but they must be used as direct substitutes for butter, and measured just as accurately. In vegetable preparation, baking, boiling, or steam pressure cooking may be used. Any fat used for seasoning these vegetables must be taken from the butter allowance.

In all cookery, salt, pepper, vinegar, saccharin, and spices may be used as desired unless there are other therapeutic restrictions on the diet. Water, black coffee, clear tea, and clear fat-free broth may be used in unlimited quantities.

Two supplements which we use for desserts are the diabetic gelatin called D-Zerta which has so little food value that it is negligible, and Junket tablets containing no food value, but which will congeal milk to a soft custard consistency. The use of all other special foods, such as diabetic puddings (so-called), diabetic cookies, and candies, is discouraged. If a patient insists upon using them, we ask them either to check the product or the label so that the food values can be computed.

Menus are not written for our patients. We urge them to write their own, and then to let us go over the menus with them. The primary reason for this is that it helps make the diet as flexible as possible. A general outline will permit each patient to fit his food prescription to his individual budget, to make the most of his marketing facilities, and to appease his own appetite within reason.

The most important objective is to teach each diabetic patient the importance of his diet, and then to make him want to learn and understand it.

SOME PATHOLOGIC ASPECTS OF DIABETES

John B. Hazard, M.D.

Though diabetes may produce very striking changes in many tissues of the body, the organ responsible for the production of insulin may show relatively little or no change. This was even a more common finding before methods were developed for separation of the alpha and beta cells of the islets.

Though there may be no demonstrable pathologic change in the pancreas, in a large percentage of cases abnormalities may be found if special technics are used in addition to routine procedures. The beta cells of the islets can be estimated only after special fixation and a staining procedure such as that of Gomori. Since the satisfactory fixatives for this are not in common use in most pathologic departments review of much of the material collected in the past cannot be evaluated in this respect. However, when such studies have been made, beta cells have been found to be absent, greatly reduced, moderately reduced or normal. In a recent series reported by Bell (Proc. Am. J. Path 22:

631, 1946), the beta cells were absent or greatly reduced in 21 of 30 cases of diabetes. Gomori (Am. J. Path. 17:395, 1941) reports a marked reduction in the beta:alpha ratio. A second more common finding in the pancreas is hyalinization of the islets which may occur in 30 to 50 per cent of the cases, depending somewhat upon the patient's age. In older patients, of course, it may occur without the presence of diabetes. A third and much less common histologic lesion is nuclear pyknosis in the islet cells. Uncommon diseases which may be associated with diabetes are hemachromatosis, extensive carcinoma of the pancreas or even, more rare, large cyst adenoma of the pancreas.

The increase in the incidence of arteriosclerosis in diabetics is well known. Involvement of the coronary arteries results in four times as many deaths due to arteriosclerotic lesions of these vessels as are found in non-diabetics in corresponding age groups. The increased arteriosclerotic involvement of coronary arteries also reverses the sex ratio in regard to myocardial infarction.

In the peripheral arteries, reduced blood supply leads to gangrene, intermittent claudication, and probably contributes to an increased susceptibility to infection so that minor injuries to the skin may lead to serious suppurative disease. The occurence of suppurative tenosynovitis with extension of exudate along the tendons of the foot and into contiguous soft tissues is one of the serious results of the reduced ability to combat bacterial intrusion.

In the original series of 8 cases of intercapillary glomerulosclerosis reported by Kimmelstiel and Wilson (Am. J. Path. 12:83, 1936), all patients were middle aged, diabetics with hypertension, albuminuria and edema. There have been many others recorded since and the facts may be summarized: approximately 40 per cent of diabetics exhibit the lesion in some degree; in a severe degree it occurs only in diabetics. The incidence appears to increase with the duration of diabetes. Though hypertension was reported originally in all cases, subsequent reports indicate only 50 per cent with hypertensive disease. Grossly, the renal lesion much resembles that found in arteriolar nephrosclerosis, with pallor of varying degree and with a coarsely pitted surface and thin cortex. Histologically, it is characterized by small hyaline foci between the capillaries of the tuft, of varying size and number. Since amyloid is deposited in a similar location, it must be differentiated by a special staining technic to avoid possible misinterpretation of the nature of the intercapillary substance.

Acute renal infection is the cause of death in diabetics about four times as frequently as it is in a corresponding nondiabetic group. In a small portion of patients with diabetes, approximately 3 per cent as judged by past reports, a diffuse necrotizing lesion involves the renal papillae. It is of serious import as most all the patients have died, though this may be altered by modern chemotherapy. In its gross aspects, the lesion is manifest by dull, grayish to yellowish, necrotic renal papillae with sloughing tissue masses that are shed into the renal pelvis and thus produce a defect which may be evident on pyelographic examination. Histologically, there is diffuse necrosis of the tissue of the papillae, without cellular reaction or with a reaction almost limited to plasma cells. The agent is most often Staphylococcus aureus. Women develop the lesion more commonly than men.

The peripheral nerves in a small percentage of diabetics show diffuse or patchy degenerative changes associated with sclerosis of the intraneural vessels. There may be a neurolemmal proliferation. The symptoms are generally sensory, and are usually referable to the lower extremity. Trophic lesions are, of course, common in those who develop this neural lesion.

Changes in the bones and joints of the feet consist of periarticular thickening, and destruction of bones and joints so that metatarsal or phalangeal bones may be represented merely by small bone spicules lying in a fibrous matrix.

Diabetic retinopathy is among the more serious lesions occurring in diabetes. It involves the veins and capillaries of the retina as distinguished from the arterial lesions evident in hypertensive disease. The changes consist variously of venous congestion, hemorrhages, phlebosclerosis, over-growth of new veins (retinal pannus), deposition of lipoid in the nerve fiber layer and exudates of varying type and severity in the deep retinal tissues. Later in the disease there is detachment of the retina, degenerative changes in the retina and a thick vascular network. Cholesterol may be deposited in the vitreous and in the fluid beneath the retina. There is irreversibility of the more severe changes.

In typical form cataracts occur bilaterally and in severe diabetes; early it may be a reversible disease. There is opacity of the lens due to subcapsular degeneration, "water fissures" and repair proliferation.

CHOICE OF INSULIN PREPARATION

E. Perry McCullagh, M.D.

From a practical standpoint, there are four types of insulin from which to choose. They are:

1. Protamine-zinc insulin.
2. Regular and crystalline insulin.
3. Insulin mixtures.
4. Globin insulin.

Protamine-zinc insulin, first introduced in 1936 by Hagedorn, is the most popular insulin. Zinc originally added to increase the stability of the mixture has been found to prolong its effect. A single injection of this insulin is active in three or four hours and acts for more than twenty-four hours.

Regular (amorphous) and crystalline insulin have similar effects. They represent the true hormone, active within a few minutes, with a peak effect in four hours and action from a single dose which is over in about eight hours. Larger doses have relatively longer effects and concentrations as high as 500 units have prolonged activity approximating that of protamine-zinc insulin. Regular or crystalline insulin is the insulin of choice in emergencies such as acidosis, infection, trauma, surgery, and other complications.

Mixtures of protamine-zinc insulin and regular insulin have been used because it is found frequently that protamine-zinc insulin alone may fail to control blood sugar levels within the first few hours after administration. All mixtures produce modified effects of both. A new insulin mixture, designated N.P.H. 50, is being examined with the thought of having a ready-made preparation generally available.

Globin insulin is of less practical value than the others, failing often to control blood sugar levels in the first few hours after it is prescribed. If given in the morning, it tends to cause hypoglycemia in the midafternoon and may still fail to maintain normal fasting blood sugar levels.

The available glucose of the diet may be distributed by meals to meet the timing of the maximum insulin effect. We use the following distribution:

Regular or crystalline insulin	30	35	35	
Protamine-zinc insulin	20	30	40	10 H.S.
Mixtures	Any distribution suited to the individual			
Globin insulin	20	40	10 (p.m.)	30

Who Needs Insulin?

Among those who usually need it are the following:

1. Patients in acidosis.
2. Those with acute infections.
3. Patients with chronic infections.
4. Most diabetic children.
5. Patients requiring a high caloric diet.
6. Those with initial blood sugar levels over 300 mg. per cent.

Some may do as well without insulin as with it, although the number is relatively few. They include:

1. The very old patient.
2. The extremely mild diabetic.
3. The obese patient willing to follow a reducing diet who has a blood sugar level of 200 or less fasting.

Some Principles in the Use of Insulin

If the fasting blood sugar level remains high on the prescribed diet protamine-zinc insulin may be given and increased to produce a normal fasting level. Relatively smaller doses must be given to the very young, the very old, and the emaciated patient. If the fasting sugar is normal and the blood sugar level rises above normal at noon or later, regular insulin may be added as a separate dose or in a suitable mixture adjusted to individual needs.

Globin insulin is most useful in those patients with normal fasting sugar levels and high levels later in the day. In erratic diabetes in which control is unpredictable extra insulin may be added according to urine sugar if it is judged on specimens obtained within a half hour after having emptied the bladder. Formulas for patient use refer to the yellow, orange or red Benedict's tests, and may be written $\frac{\text{Y O R}}{3\ 4\ 6}$ or increased to any necessary amount such as $\frac{\text{Y O R.}}{5\ 10\ 15}$ No extra insulin is given at bed time if protamine-zinc is used.

INSULIN MIXTURES

*M. Irving Sparks, M.D.**

The purpose of insulin mixtures is to provide an "intermediate" insulin so that patients may be controlled by one daily injection. By mixing varying proportions of regular and protamine zinc insulins a graduated series of "intermediacy" can be obtained— extending from almost pure regular insulin effect on the one extreme to pure protamine zinc insulin effect on the other. The action of mixtures is that of an "intermediate" insulin, not merely a summation of the actions of its component parts.

There are four preliminary explanatory points. A. Protamine Zinc Insulin—protamine and insulin combine chemically, therefore in definite proportions (0.67 mg. of protamine per 100 units of insulin). But in the commercial preparation of P.Z.I., the manufacturers add almost twice as much protamine as is necessary (1.25 mg. protamine per 100 units). It therefore follows that commercial P.Z.I. can take up and convert to P.Z.I. almost its equivalent in unitage of regular insulin. In other words, 10 units P.Z.I. + 10 units regular = 20 units P.Z.I. This is not strictly accurate, but it is close enough to allow of the general rule—that to obtain any intermediate effect, there must be at least as much regular as protamine zinc insulin (by units) in the mixture.

B. Mixtures of two types have been recommended, and either one is indicated only when protamine zinc insulin by itself is not adequate.

1. Fixed Mixtures—when mixtures are indicated some workers have advocated using only one of the possible variations. Mixtures of 3:2 or 2:1 (regular: P.Z.I.) are the ones most recommended.

2. Variable Mixtures—here the proportions used are varied according to the needs of the individual patient. And the needed proportions vary widely not only from patient to patient, but in the same patient from time to time.

Each diabetic patient presents an individual problem which can be met better with a flexible than with a fixed method. Variable mixtures are therefore preferred.

One further point in favor of "variable" as opposed to "fixed" mixtures is mentioned under diet.

C. Diet—the diet used for "mixtures" is the same as for protamine zinc insulin alone, namely three approximately equal meals and a bed-time feeding. Breakfast may be made smaller if desired. With "fixed mixtures" it is more often necessary to use a mid-afternoon feeding than with "variable mixtures." Indeed with the latter it is only rarely required.

D. Method of checking—the one found to be the best is the one advocated by Dr. H. John, for it gives the picture throughout the day. It consists of taking sugar before each of the main meals (three a. c. blood sugars) on the day of check. The patient should be on any one given dose of insulin for at least two days before the check is made.

The procedure of regulating diabetes is as follows:

1. Put on adequate diet.
2. Then three a. c. blood sugars.
   a. if these adequate—no further treatment.
   b. if these high—put on 20 or 30 units P.Z.I.
3. Then three a. c. blood sugars
   a. if all about same level continue P.Z.I. increasing by 10 to 20 units at time until desired level of blood sugars is obtained.
   b. if spread of more than 100 mg.—change to mixtures. This applies regardless of the actual height of the blood sugars.

Graphs were shown illustrating the use of mixtures from which the following rules were deduced.

1. Use more regular than protamine zinc insulin.
2. The fasting blood sugar is the indicator as to whether the P.Z.I. should be increased or decreased.
3. The noon and afternoon blood sugars are the indicator for increasing or decreasing the regular insulin.

The first rule is not an invariable one, for occasionally patients are seen who obtain an intermediate effect from mixtures containing less regular insulin than P.Z.I.

Variable mixtures may be made up in either of two ways.

1. In the syringe each morning.
2. The proper amounts of each sufficient for 10 to 20 doses put into a bottle; the daily total dose being withdrawn each morning.

Most patients seem to prefer the former method, nor have any of them had any technical difficulty in using the mixtures.

Mixtures are needed more frequently when the total dose is over 30 units per day. But they have been used to advantage in total doses of from 15 to 90 units.

Almost 90 per cent of diabetic patients needing insulin can be adequately controlled by one injection a day. Fifty per cent by P.Z.I. alone, the remainder by mixtures.

*By invitation. 10515 Carnegie Avenue.

COMPLICATIONS RESULTING FROM INSULIN ADMINISTRATION

A. Gold, M.D.

Complications resulting from insulin administration are:

I. Physiological
   - A. Hypoglycemia
   - B. Insulin edema
   - C. Insulin presbyopia

II. Abnormal
   - A. Allergic
     1. Local
     2. General
   - B. Infection
   - C. Etiology unknown
     1. Insulin hypertrophy
     2. Insulin atrophy
   - D. Insulin resistance

The education of the diabetic patient in the recognition of and preparedness for hypoglycemia is important. Danger of permanent brain damage from prolonged insulin coma must be kept in mind.

Obese patients not infrequently complain of symptoms resembling those of hypoglycemia when, in fact, the blood sugar is normal or elevated. This should be demonstrated to the satisfaction of patient and doctor by doing blood sugar estimations during any suspected reactions.

In the absence of glucose for intravenous use, the patient in insulin coma may be given epinephrine in 1 c.c. dosage.

General or local edema of the face may occur shortly after beginning insulin treatment, especially in severe diabetics. This is due to rapid changes in water and mineral metabolism associated with the improved carbohydrate metabolism and subsides spontaneously. Changes in refraction are due to the same cause.

Localized swelling, pain, and tenderness at the site of insulin injection occurs frequently during the first few weeks of insulin treatment. The technic of injection should be gone over with the patient to establish whether he has been giving himself injections partially intradermally rather than subcutaneously. If such reactions persist after several weeks, crystalline insulin alone should be tried and in the strongest concentration available.

Anaphylactic reactions to insulin are fortunately extremely rare. The acute attack should be treated with intramuscular epinephrine, ½ c.c. repeated in twenty minutes if necessary. This should be followed by the use of an antihistamic such as pyribenzamine. Desensitization should be started as soon as possible. The rapid technic consisting of intradermal injections every fifteen minutes beginning with 1/1000 unit and doubling the dose each time unless a wheal appears when the last dose is repeated. When 1 unit can be given intradermally without wheal formation, subcutaneous injections should be started.

Insulin hypertrophy and atrophy are local reactions occurring in the subcutaneous tissues in areas in which insulin has been injected repeatedly. They may be avoided by teaching the patient to vary the site of injection according to a definite routine.

Insulin resistance may be associated with infection, acidosis, hormonal antagonists, allergy, or diffuse hepatic disease. Signs of hyperthyroidism, acromegaly, Cushing's syndrome and pheochromocytoma should be looked for. In spite of all investigations possible, in a majority of cases the cause remains undetermined. It is important to give

as much insulin as needed—which has been known to go as high as 2000 units daily—to prevent ketosis. *U500* insulin is helpful when dosage is high. Not infrequently resistance subsides spontaneously over a period of months.

PANCREATIC DISEASE AND DIABETES

Charles H. Brown, M.D.

The pancreas is intimately related anatomically and physiologically to the liver and may be said to be its guardian. Depancreatized dogs, patients with pancreatic steatorrhea, diabetic patients, particularly the juvenile type, frequently have fatty infiltration of the liver. Adequate doses of lipotropic substances such as lecithin, choline, and methionine, and the pancreatic hormone lipocaic decrease this fatty infiltration.

The relationship of disease of the pancreas to diabetes has long been and still is a major problem. The discovery of insulin was believed by many to have solved this problem. This is not the case as is shown by the fact that a considerable number of diabetics require more insulin than the 30 to 50 units required by patients who have had complete pancreatectomies.

The relationship of carcinoma of the pancreas to diabetes presents two problems. First, it is unlikely and rare that carcinoma of the pancreas causes true diabetes, although there may be changes in the glucose tolerance curves due to malnutrition, impaired liver function or other factors. Second, carcinoma of the pancreas does occur more frequently (4 to 6 times) in diabetics than in non-diabetic patients. The relationship of carcinoma of the pancreas to diabetes is similar to the relationship of carcinoma of the liver to cirrhosis.

Pain is present in about 80 per cent of the patients with carcinoma of the pancreas. Jaundice is present in about two-thirds of the patients; loss of weight is rapid and pronounced. Fatigue, weakness, nausea or vomiting, anorexia and constipation are other symptoms that are present in about one-half the cases. Diarrhea and psychoneurotic symptoms are present in about 10 per cent of the patients. Thrombophlebitis is common in this disease. On physical examination, a gallbladder is palpable in about one-third of the cases, a mass in about 15 per cent and ascites in about 15 per cent. Roentgen-ray examination may show: 1. widening of the duodenal loop. 2. inverted figure 3 sign and deformities of the second part of the duodenum, and 3. displacement of the stomach and other organs.

Calculus formation in the pancreas as a cause of diabetes is uncommon. However, diabetes is present in one-third to one-half of the patients with pancreatic lithiasis. Pain is usually present and is apt to be severe. Steatorrhea exists in about one-half of these patients. The clinical diagnosis is entirely dependent on the demonstration of opacities in the region of the pancreas on the x-ray film.

Acute pancreatitis is frequently accompanied by transient changes in the glucose metabolism and in transient glycosuria. Approximately 2 per cent of patients with acute pancreatitis will develop permanent diabetes. There are many milder cases of acute pancreatitis that may be confused with other abdominal catastrophes that require surgery. Surgery is contraindicated in acute pancreatitis, since 50 per cent of those subjected to surgery during the acute stage die. Consequently, it is advisable to obtain routinely serum amylase or diastase determination on every patient who has an abrupt onset of upper abdominal pain.

Chronic pancreatitis is an ill-defined clinical entity in which there is chronic fibrosis of the pancreas due to a diverse variety of conditions. Biliary tract infection, duodenal ulcer, obstruction of the pancreatic ducts by calculi or neoplasm, chronic alcoholism, hepatic cirrhosis, acute infection, and acute pancreatitis may all cause chronic pan-

creatitis. One might suspect this condition in any patient who has three of the following: 1. diabetes, 2. large voluminous stools, 3. severe loss of weight and 4. jaundice.

Serum amylase or diastase are uniformly elevated in acute pancreatitis in the first forty-eight hours. Serum lipase is elevated in acute pancreatitis and in about 40 per cent of the cases with carcinoma of the pancreas. Stool examination may show an increase in the unsplit fat and in the nitrogen content. In carcinoma of the pancreas duodenal drainage shows an absence of bile and the presence of blood and occasional tumor cells, while double tube intubation shows a decrease in pancreatic enzymes in carcinoma of the pancreas. Urinalysis, blood sugar determinations, and glucose tolerance tests will frequently show frank diabetes or impaired glucose metabolism in patients with pancreatic disease.

GLUCOSE METABOLISM IN LIVER DISEASE

H. R. Rossmiller, M.D.

Endogenous glucose is derived from the liver either from glycogen stores or fats and protein. The liver can manufacture glucose from the glycerol portion of the fat molecule and certain amino acids. These mechanisms are important in the main-molecule and certain amino acids. These mechanisms are unimportant in the maintenance of normal concentrations of blood sugar.

The proof of the central role of the liver in sugar metabolism is best demonstrated by hepatectomy which rapidly produces hypoglycemia. Acute necrosis of the liver may also produce hypoglycemia due to failure of both the glucose storage and manufacturing functions of this organ. In chronic parenchymal liver disease such as Laennec's cirrhosis hyperglycemia may be present, apparently due to failure of the glucose storage function at normal blood sugar levels.

The amount of stored glycogen in the liver, as shown by Whipple and Sperry in 1909 is important in the prevention of liver damage. Large stores of liver glycogen increases resistance to liver damage and the feeding of large amounts of dextrose in the presence of a damaged liver accelerates recovery. The factors which influence the amount of glycogen in the liver are therefore of considerable importance.

Diet, the source of exogenous glucose, alters the amount of glycogen contained in the liver cells. Starvation depletes the glycogen reserve of the liver. High fat diets produce a similar effect and at the same time will cause a great deal of fat to be deposited in the hepatic cells. Conversely a high carbohydrate diet favors glycogen storage in the liver. A high protein diet produces a similar effect apparently by increasing manufacture of glucose from the source.

Various secretions of the endocrine glands particularly adrenalin, insulin and anterior pituitary extracts alter the amount of glycogen in the liver. Diminution of hepatic glycogen occurs when the liver cells are damaged by such toxic agents as chloroform, arsenic and phosphorus. Hepatotoxic agents are thought to act first as an irritant to the glycogenolytic mechanism of the liver, i. e. increase glycogen formation and favor depletion of the store.

After ingestion of carbohydrate in normal persons the blood sugar level rises and as this occurs glycogenesis begins with the aid of optimum insulin secretions. However extra insulin does not influence the deposition of glycogen in the liver. This observation is of importance as it pertains to patients who have hyperglycemia due to liver disease and who have a normal insulin secreting mechanism. It does not seem likely that added insulin would prove helpful in increasing glycogen deposition in the liver.

It is desirable to increase the glycogen deposition in the liver not only in the treatment of liver disease but also in its prevention. However, the feeding of high carbohydrate diets to patients with chronic parenchymal liver disease, particularly Laennec's

cirrhosis, may result in hyperglycemia and glycosuria. This should not deter continuation of such treatment for it has been shown by Cori and Cori that the level of the blood sugar concentration is all important in determining the rate of glycogen deposition in the damaged liver.

DIABETIC COMA

*Edmund E. Beard, M.D.**

Diabetic coma is the most serious complication of diabetes mellitus, as it is almost invariably fatal if not adequately treated. Since the advent of insulin coma has become to a large extent avoidable and much more amenable to treatment.

Understanding of its pathogenesis has contributed greatly to improvement in prevention and treatment of coma. The outstanding events in its development are:

1. Decrease in insulin effect, such as in failure of the diabetic to take his insulin, or insensitivity to insulin as may occur in infections.
2. Decrease in utilization of carbohydrate. Combustion of fat is increased.
3. Increase in ketone production. These are the normal products of the catabolism of fatty acids, not in themselves pathologic, but as a consequence of "2," they accumulate at an enormous rate. As they are acid they must be excreted. To do this the body must sacrifice base.
4. Alkali reserve reduced.
5. Sodium is lost, excreted as no-ketone salt.
6. Water goes with sodium—dehydration occurs.
7. Eventually shift in Ph of the blood to the acid side.
8. In coma there is often a progressive decrease in effectiveness of insulin.

There is no entirely satisfactory definition of diabetic coma. Certainly no single function can serve as a diagnostic criterion. We must consider the concentration of acetones in urine (and blood), the degree of depletion of alkali reserve, the degree of dehydration, and the degree of consciousness. The appearance of acetone in the urine of the diabetic is a danger signal, and calls for treatment.

Precipitating factors of coma are: 1. acute infection, 2. omission of insulin, 3. vomiting and diarrhea, 4. prolonged lack of good control, 5. indiscretion in diet, 6. operations, 7. pregnancy, 8. thyro-toxicosis and other endocrine disturbances, 9. insensitivity to insulin.

The onset may be insiduous and variable. Increasing listlessness, loss of appetite, dryness of mouth, throat and tongue, polydipsia and polyuria are common. Symptoms of poorly controlled diabetes are followed by those more specific of acidosis: nausea, vomiting and diarrhea, pain in abdomen, drowsiness, air hunger and loss of consciousness.

The patient looks desperately ill. There is air-hunger (in extremis respirations may become rapid and shallow) and acetone odor on the breath and severe dehydration. The skin is cool and dry. Mucus membranes and tongue are dry. Eyeballs are soft. The temperature usually is low, even with infection. Blood pressure is low: the pulse rapid and soft.

Blood sugar is usually 400-800 mg./100 cc. More important is increase of acetone in urine and blood, which latter is the real index of danger from ketosis per se (it may increase while the carbon dioxide combining power of the blood is returned to normal by administration of alkali.) Carbon dioxide combining power is low, usually below 20 vols. per cent. The urine is of high specific gravity and contains sugar, acetone, albumen and casts. In the blood, cholesterol, fat, and non-protein nitrogen are in-

creased, sodium chloride is decreased. Red count hemoglobin and hematocrit are high. The white blood count is increased beyond the effect of hemoconcentration.

Infection should always be in mind because it is often present, may be not readily apparent, and is of high importance. Furuncles, gangrene, pneumonia, otitis media, and urinary infections especially should be sought, and should be treated on suspicion.

Two syndromes likely to be mistaken for diabetic coma are hypoglycemic coma and cerebral accident. In both the history is important, there will be no dehydration and there probably will be no acetone in the urine. If there is any doubt, intravenous glucose, *not* insulin, should be given.

The prognosis is good if the patient is young, only drowsy, if blood pressure is not low, if there is no complicating infection, if the carbon dioxide is low in amount. It is grave if the patient is over 40 years, if completely unconscious for over twelve hours, if the systolic blood pressure is under 50 mm. Hg., if severe infection is present, if there is anuria and severe nitrogen retention, if there is much cardiovascular disease, if the blood sugar is over 1000 mg./100 cc. and if treatment is not vigorous.

Preventive treatment includes elimination of acetone from the urine. Insulin should not be omitted when the patient cannot take food unless there is no acetone and the blood-sugar is low or the urine sugar free.

The treatment of coma includes: 1. Insulin, the specific. Initial dose will vary from 50 U in the mild to 200 U in the very severe cases, given half and half subcutaneously and intravenously (to guard against failure of absorption). Never rely on intravenous dosage alone. Follow-up doses are given every two to four hours in amounts varying with the rate of improvement. If there is no sign of improvement in four hours, high dosage must be maintained or increased, as in some cases insulin may be completely ineffective. Cases of recovery are reported after the use of over 5000 U in twenty-four hours.

Protamine insulin should never be used alone in the treatment of coma; it may be used in part. One must remember that there may be rapid increase in the effectiveness of insulin as improvement occurs. It is for this reason that we prefer to use protamine insulin in doses not to exceed 40-50 U as an initial dose.

2. Fluids. Normal saline given in amount needed to restore kidney function and eliminate dehydration. Figure usually about 5 per cent of body weight, 30-40 Gm. of sodium chloride.
3. Glucose. Given as 5 per cent solution with the saline as needed to prevent hypoglycemia. Almost never necessary in first few hours; it may operate to slow dehydration by maintaining high blood sugar and high diuresis; 100 Gm. or more in first 24 hours.
4. External warmth, using great care not to burn. Gastric lavage and enema, often recommended, can usually be omitted, or at least deferred.
5. Food. As soon as consciousness is regained. Valuable as a source of carbohydrate and of vitamins and minerals, perhaps potassium especially.
6. Alkali. Its only indication is severe hyperpnea with carbon dioxide combining power below 20 vols. per cent. The mere restoration of this level to normal confers no benefit. Ringer's solution or Lactate Ringer's solution may be used for this purpose and it has the advantage of containing some potassium, which offers protection against hypopotassemia, undoubtedly in some instances a complication of the treatment of diabetic coma, though we have not yet recognized it in any of our cases.

*By invitation. 13224 Shaker Square.

(*To be concluded in the next issue*)

ANNOUNCEMENTS

Bunts Course

The Bunts Institute will present a two and one-half day course on "Medical and Surgical Disorders of the Urinary Tract" at the Cleveland Clinic on November 17, 18, and 19. Dr. Herman L. Kretschmer of Chicago will be the guest speaker on Thursday evening, November 17. On Saturday morning, November 19, Dr. Louis Leiter of New York will talk on uremia. The course will close with a Panel Discussion ending about noon on Saturday. Registration is open to any graduate of an approved medical school. The fee is $15.00. A full program will be published in the October Cleveland Clinic Quarterly. Inquiries may be directed to Edwin P. Jordan, M.D., Director of Education, Cleveland Clinic Building, 2020 East Ninety-third Street, Cleveland 6, Ohio.

Lower Fellowship Thesis Prize and Certificates

The 1949 Lower Fellowship Thesis Prize was awarded on June 20 to Dr. Richard S. Graves for his paper entitled "Epididymitis, Its Production by a Physical Agent (Sterile Urine) in the Vas Deferens." This prize was established in 1935 by Dr. William E. Lower, one of the four founders of the Cleveland Clinic who died June 17, 1948.

At the same ceremony certificates were awarded to 14 fellows who had satisfactorily completed their formal training in various specialty fields. These were Drs. J. T. Bakody, H. L. Browns, H. H. Fertig, W. K. Hokr, S. R. La Tona, W. B. Leffler, J. D. Loudon, C. J. McGarvey, B. E. Mulvey, J. P. Proudfit, R. B. Turnbull, E. C. Weiford, J. F. Whitman, and R. E. Wise.

Bunts Lecture

Dr. Austin E. Smith, secretary of the Council on Pharmacy and Chemistry and assistant editor of *The Journal of the American Medical Association*, will give the first 1949–50 Bunts lecture on the subject of "Modern Trends in Drug Therapy." This will be held at 8:15 p.m. on Monday, September 26, in the Founders and Staff Room. Dr. Smith's lecture will also open the basic science course for fellows which was inaugurated last year.

THOMAS E. JONES, M. D.
Chief of Staff of Surgery

Born April 1, 1892
Died September 29, 1949

ON Thursday morning, September 29, 1949, the Clinic was shocked by the sudden death of Dr. Thomas E. Jones. Dr. Jones at the time of his death was getting into his operating clothes in preparation for his usual, heavy surgical schedule. Although he belonged to many professional organizations and had served actively in many of them, only those who knew him closely could appreciate his devotion to his patients and to the cause of his profession.

Dr. Jones was born in Wales on April 1, 1892. He and his family came to this country while he was a small boy. He attended high school in Steubenville, Ohio, and Adelbert College of Western Reserve University. His medical degree was obtained in 1916 from Western Reserve University Medical School. He served in the Medical Corps of the field artillery in World War I. He was not married.

Dr. Jones was one of the original members of the staff of the Cleveland Clinic Foundation serving that institution continuously since February 1921. Patients, colleagues, and friends as well as the institution to which he contributed so much will suffer from his absence.

DIAGNOSIS AND TREATMENT OF THE CARDIAC ARRHYTHMIAS

A. CARLTON ERNSTENE, M.D.
Division of Medicine

DISTURBANCES of the rhythm of the heart comprise one of the most common problems in clinical cardiology. They may occur as a complication of organic cardiac disease or in the entire absence of a structural abnormality of the heart. Certain arrhythmias are of no significance although they often cause disagreeable symptoms. Others result in an important reduction in the mechanical efficiency of the heart and may precipitate congestive myocardial failure or intensify pre-existing decompensation. Still others, among the more uncommon disorders, constitute a direct threat to life. Accurate diagnosis is essential not only for appropriate treatment but also for correct estimation of the clinical importance of the condition. Fortunately, most of the arrhythmias can be recognized by physical examination alone. Electrocardiographic corroboration of the diagnosis is always desirable, however, and a few of the disturbances can be identified only by instrumental means.

Premature Beats

Premature beats, the most common type of cardiac arrhythmia, may arise from the auricles, ventricles, auriculoventricular node or main stem of the bundle of His. They are of clinical significance only in exceptional instances although they not infrequently cause uncomfortable symptoms due either to the pause which follows the premature beat or to the unusual force of the next normal ventricular contraction. Patients frequently report a sensation that the heart has stopped momentarily or skipped a beat. Occasionally, in sensitive persons, there may be fleeting lightheadedness, a choking sensation in the throat, or transient pain in the precordial or substernal area.

Premature beats usually can be recognized without difficulty by auscultation of the heart. The dominant cardiac rhythm is regular but is disturbed, at frequent or infrequent intervals, by a beat which comes before its expected time and is followed by a pause. If the beat is exceptionally premature it may fail to cause a perceptible pulsation in the radial artery. Auricular and nodal premature beats disturb the basic rhythm of the sinoauricular node and because of this the pause which follows them is not completely compensatory. The interval between the normal beat preceding the early beat and the first normal response after the premature systole is less than the length of two normal cycles. In ventricular premature beats, on the other hand, the rhythm of the normal pacemaker is not disturbed, and the compensatory pause is complete. Although one may at times estimate the completeness of the compensatory pause with fair accuracy by auscultation, the electrocardiogram is necessary for positive differentiation of the various types of premature beats.

Auricular premature beats are characterized electrocardiographically (fig. 1) by P waves which differ in form from the P waves of the patient's normal beats and are often inverted or diphasic. The P-R interval is usually longer than 0.10 seconds. The QRS complexes generally are similar to the normal QRS complexes, but if the premature beat occurs before the bundle branches or ventricular musculature have recovered from their refractory period, distinctly aberrant complexes may result.

In nodal premature beats (fig. 2), the P waves also are of abnormal form but differ from the P waves of auricular premature beats in that they may occur after, during, or before the QRS complex. When they precede the QRS complex, the P-R interval is less than 0.12 seconds. The QRS complexes usually are similar to those of the normal beats.

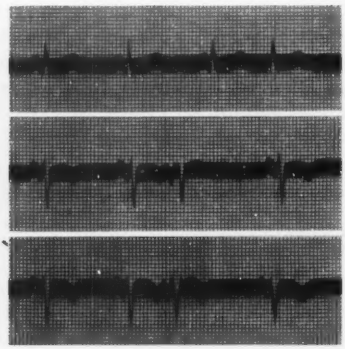


FIG. 1

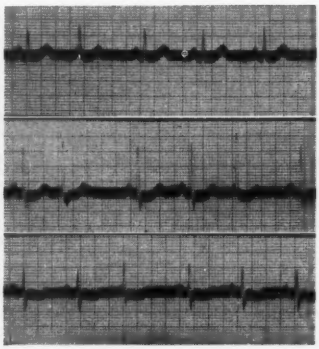


FIG. 2

FIG. 1. Auricular premature beats. The P waves of the premature beats differ in form from that of the normal beats, but the QRS complexes show only minor alterations. The compensatory pause is incomplete.

FIG. 2. Nodal premature beats. With the exception of the first premature beat in lead II, the P waves of the premature beats fuse with the beginning of the QRS complexes.

Ventricular premature beats (fig. 3) cause abnormal, widened, slurred or notched QRS complexes which are not preceded by a P wave. Occasionally they may be interpolated between two normal cardiac contractions, in which event they constitute a true extra systole.

Since premature beats rarely are of significance, they seldom require treatment. Inquiry should be made concerning nervous tension and the excessive consumption of tobacco or coffee because control of these factors may diminish the arrhythmia or correct it entirely. In patients who are experiencing annoying symptoms or who have become concerned about the heart, reassurance is important and mild sedatives often are helpful. If symptoms persist in spite of these measures, quinidine sulfate, 0.2 Gm. (gr. 3) two or three times a day may prove of value. Potassium chloride in doses of 1 or 2 Gm. three or four times a day may also be effective but must not be administered to indi-

viduals who have renal disease. The fact that premature beats so frequently occur while a person is at rest and can be eliminated by physical activity should be pointed out, especially to apprehensive patients.

Although premature beats are observed in many normal individuals, they occur even more commonly in patients who have organic heart disease and are at times of clinical importance. The arrhythmia, for instance, may be an early manifestation of digitalis intoxication. Myocardial insufficiency is accompanied occasionally by the appearance of frequent premature beats arising from one or more foci in the ventricular myocardium. Digitalis therapy and sodium restriction may then reduce their number or abolish them entirely. In acute myocardial infarction, frequent premature beats are a potential

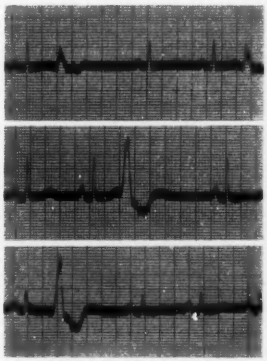


FIG. 3. Ventricular premature beats. The QRS complexes of the premature beats are wide, slurred and distinctly abnormal, and they are not preceded by a P wave. The compensatory pause is complete.

precursor of ventricular paroxysmal tachycardia, and in their presence the administration of quinidine sulfate as a prophylactic measure against the development of this more serious arrhythmia is indicated. Numerous auricular premature beats are at times a forerunner of auricular fibrillation, especially in patients who have mitral stenosis. Quinidine sulfate and sodium restriction may be of value in preventing this type of progression.

Auricular Paroxysmal Tachycardia

Auricular paroxysmal tachycardia consists fundamentally of a paroxysm of auricular premature beats and, next to premature beats, is the most common disturbance of cardiac rhythm. Characteristically, the attacks develop and end abruptly. They may last for a few beats only or for hours or days. The rhythm during the paroxysm is perfectly regular and the heart rate generally between 160 and 200 beats per minute. Although the condition occurs occasionly in persons who have organic heart disease, it is encountered most commonly in patients who present no abnormal cardiac findings.

In adults who have normal hearts, auricular paroxysmal tachycardia causes no cardiac embarrassment even if the attacks persist for days. The patient, however, is often considerably disturbed by weakness, faintness, dizziness or palpitation. In infants and in individuals who have organic heart disease, a prolonged paroxysm may result in the development of congestive heart failure, and in persons with coronary artery disease, an attack may be accompanied by substernal pain which persists until the tachycardia is controlled.

The electrocardiogram in auricular paroxysmal tachycardia (fig. 4) shows a rapid, regular succession of QRS complexes which are typically of normal contour. The ventricular rate seldom varies more than two or three beats per minute. The P waves usually are diphasic or inverted, and the P-R interval is prolonged. If no P waves are discernible, as is often the case, the condition cannot be distinguished from nodal paroxysmal tachycardia, and the term paroxysmal supraventricular tachycardia is then employed. Nodal paroxysmal tachycardia, however, is much less common than auricular paroxysmal tachycardia. The treatment of the two arrhythmias is the same.

There are a number of simple procedures which will abruptly terminate many attacks of auricular paroxysmal tachycardia. Among the most effective of these are holding a deep breath, pressure on the right or left carotid sinus, firm ocular pressure, and sudden flexion of the body at the hips. These measures either restore the heart rhythm to normal immediately or have no effect at all on the heart rate. If the tachycardia persists and the patient is in distress, drug therapy becomes advisable. The treatment of choice in such a circumstance is rapid digitalization, preferably by the intravenous route. Weisberger and Feil[1] have reported excellent results from the intravenous administration of lanatoside C in doses of 0.8 mg. (4.0 cc.) followed by a second dose of the same size when the tachycardia was still present after thirty minutes to one hour. One must, of course, be certain that persons who are to receive digitalis by intravenous injection have not received the drug in any form during the preceding two weeks.

Youmans, Goodman and Gould[2] recently reported that neosynephrin by rapid intravenous injection in doses of 0.5 mg. to 2.0 mg. will restore sinus rhythm in most cases of paroxysmal supraventricular tachycardia. The drug should not be administered to patients who have coronary artery disease or in whom hypertension is present during the tachycardia. Other preparations that often are effective are prostigmine methylsulfate, 0.5 to 1.0 mg., and mecholyl, 10 to 20 mg., repeated if necessary after thirty minutes. Both of these drugs are given by subcutaneous injection. Because of the frequency with which mecholyl causes symptoms of excessive parasympathetic stimulation, it is employed only rarely and only after a syringe containing atropine sulfate, 0.6 mg., has been prepared beforehand for intravenous use if necessary. Neither prostigmine nor mecholyl should be given to patients who have bronchial asthma, and the use of mecholyl is also contraindicated by the presence of coronary artery disease.

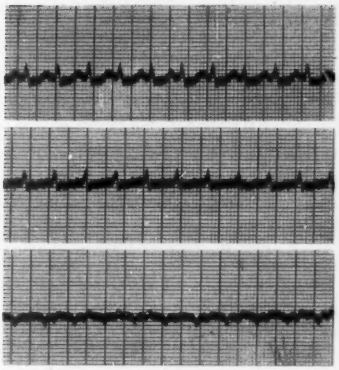


FIG. 4. Auricular paroxysmal tachycardia. There is a rapid succession of QRS complexes which are of normal contour. The rate is 188 per minute. The P waves are diphasic in leads 2 and 3, and the P-R interval is at least 0.16 seconds.

Ventricular Paroxysmal Tachycardia

Ventricular paroxysmal tachycardia is a relatively rare condition which usually is due to serious organic heart disease. It occurs most commonly as a complication of acute myocardial infarction, and in this situation it may be a forerunner of ventricular fibrillation. Occasionally, however, it is encountered in the entire absence of evidence of organic cardiac disease. As in the other types of paroxysmal tachycardia, the attacks usually are sudden in onset and termination, and the ventricular rate generally is in the range of 160 to 200 beats per minute. The electrocardiogram is necessary for certain identification of the arrhythmia, but Levine[3] has pointed out that a reliable diagnosis can be made at times from the findings on physical examination alone. Although the rhythm in ventricular tachycardia at first impression appears to be regular, an occasional fleeting irregularity often can be detected by careful auscultation. This serves to distinguish the condition from auricular paroxysmal tachycardia. Furthermore, if one listens carefully over the cardiac apex, an occasional accentuation of the first sound for a single beat frequently can be heard. In ventricular paroxysmal tachycardia, the auricles and ventricles beat independently, and the accentuation of the first sound at intervals is due to simultaneous auricular and ventricular systole. In auricular paroxysmal tachycardia, the auricles and ventricles contract in normal sequence, and the intensity of the first sound, therefore, does not vary. As an additional point in differential diagnosis, pressure on the carotid sinus does not terminate the attack of ventricular tachycardia as it does so often in auricular tachycardia.

Electrocardiographically, ventricular paroxysmal tachycardia is characterized by an uninterrupted series of ventricular premature beats occurring at regular or almost regular intervals but frequently differing slightly in form from beat to beat (fig. 5). P waves occur at their normal rate but it may be

possible to recognize them only here and there. Unless P waves can be identified and the auricular rate estimated, a definite diagnosis of ventricular tachycardia cannot be made, for paroxysmal supraventricular tachycardia with aberrant QRS complexes and indiscernible P waves will produce a similar electrocardiogram.

Quinidine sulfate is the most valuable drug in the treatment of ventricular paroxysmal tachycardia. Although it can be given by intravenous injection, the oral route is used most commonly because of its greater safety. A number of different dosage schedules have been recommended. One that has proved satisfactory consists of the administration of 0.2 Gm. as a trial dose, followed by 0.4 Gm. every two hours until the ventricular rate slows to 120 per minute. Gold[4] advises that, when the rate has been reduced to this level, the electrocardiogram be repeated in order to determine whether or not auricular activity is present. If it is, the administration of the drug is continued until normal rhythm is restored. If no P waves can be seen, on the other hand, the dose of quinidine is reduced and the interval between doses lengthened in such a manner as to maintain a rate of approximately 120 beats per minute. Electrocardiograms are made at intervals of two to four hours, and the original schedule of dosage is not resumed until P waves reappear in the tracings. This is done to avoid a period of complete cardiac asystole when the arrhythmia is brought to an end.

When quinidine sulfate fails to terminate a paroxysm of ventricular tachycardia, the intravenous administration of 10 cc. of a 20 per cent solution of magnesium sulfate may reestablish sinus rhythm.

Auricular Fibrillation

Although auricular fibrillation may occur in young individuals as a purely functional disorder, it usually is associated with organic cardiac disease, especially rheumatic heart disease with mitral stenosis. It is a not infrequent complication of thyrotoxicosis and may also develop during the course of pneumonia and certain other febrile illnesses. In it, there is complete incoordination of the contraction of the muscle fibers of the auricles. Auricular systole is abolished, and the auriculoventricular node is showered by a rapid, irregular succession of impulses from the auricles. Ventricular contractions occur in response to a variable number of these, and a completely irregular ventricular rhythm results. Ventricular responses which follow the preceding systole by a very brief interval often fail to cause a pulsation in the peripheral arteries, and a pulse deficit results. It is the absolute irregularity of the heart, however, and the entire absence of an underlying basic rhythm that constitute the pathognomonic features of the disturbance.

Auricular fibrillation can be recognized without difficulty as long as the ventricular rate is elevated, but when the rate has been reduced by digitalis or is naturally slow, careful auscultation may be necessary to distinguish the condition from the arrhythmia of premature beats. A helpful point in differential diagnosis consists of the fact that with premature beats a long pause is

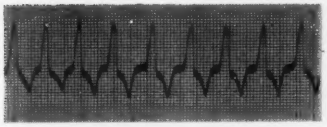


FIG. 5. Ventricular paroxysmal tachycardia. The QRS complexes are wide and slurred, and the rhythm is not quite regular. The ventricular rate is 140 per minute. Only a rare P wave can be identified.

always preceded by an early beat, but in auricular fibrillation such pauses often occur without shortening of the interval between the two preceding beats.

In the electrocardiogram of auricular fibrillation (fig. 6), the rhythm of the ventricles is completely irregular and the P waves are replaced by small, irregular, variable deflections, known as f waves, which usually have a rate of 400 to 450 per minute.

The presence of auricular fibrillation is always an indication for the administration of digitalis. When the ventricular rate is elevated, the drug is given in sufficient amounts to reduce the rate at rest to approximately 70 beats per minute. In the presence of hyperthyroidism, however, it is seldom possible to accomplish this degree of slowing before the appearance of symptoms of digitalis overdosage, and one should be content with ventricular rates between 90 and 100 per minute. Even when the ventricular rate is naturally slow in auricular fibrillation, digitalis is indicated in amounts sufficient to accomplish theoretical digitalization. This procedure usually does not cause further slowing of the ventricles but is recommended as a measure to prevent an undue rise in heart rate during physical activity or infections.

Digitalis does not possess the property of re-establishing normal rhythm in patients who have auricular fibrillation. Quinidine sulfate is employed for this purpose but the indications for its use are quite limited. It is of greatest value in cases in which the arrhythmia has developed as a complication of

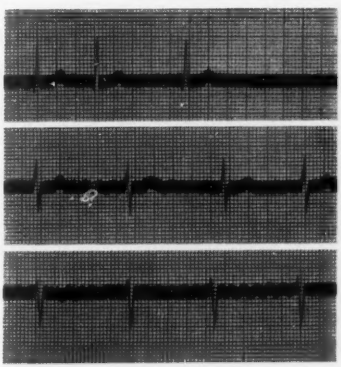


FIG. 6. Auricular fibrillation. The P waves are absent and have been replaced by small, irregular f waves. The ventricular rhythm is completely irregular.

hyperthyroidism and persists after the thyrotoxicosis has been controlled by thyroidectomy, propyl thiouracil or radioactive iodine. Quinidine can be employed also in cases of auricular fibrillation due to organic heart disease when the arrhythmia is known to be of recent origin and is not associated with mitral stenosis, congestive heart failure or more than slight cardiac enlargement. A history of an earlier embolic accident contraindicates its use. Administration of the drug should be preceded by complete digitalization, and maintenance amounts of digitalis should be given throughout the period of therapy. The patient must be kept under close observation and should remain in bed each day until two hours after the last dose of quinidine. The best results seem to be obtained when the drug is given with an interval of two hours between doses. On the first day, two doses of 0.2 Gm. are administered as a test for possible hypersensitivity. If no symptoms develop, five doses of 0.4 Gm. are given on each of the following days, but if auricular fibrillation is still present at the end of five days, the drug is discontinued.

Auricular Flutter

Auricular flutter is much less common than auricular fibrillation and rarely occurs in the absence of organic heart disease. It is due to essentially the same type of auricular disturbance as auricular fibrillation but with the difference that regular auricular contractions of limited extent occur at a rate in the neighborhood of 300 or 350 per minute (fig. 7). Because a certain degree of auriculoventricular block is almost always present, the ventricular rate is slower than the auricular. When the degree of block is constant, the ventricular rhythm is regular, but when the block varies, an irregular rhythm results. If the auriculoventricular block is constant and of such a degree as to give a ventricular rate within the usual limits of normal, the presence of auricular flutter may be overlooked and first discovered only when an electrocardiogram is taken because of associated organic heart disease. Occasionally, in cases of this kind, however, careful inspection of the venus pulsations in the neck may reveal three or four or even more auricular pulsations to each ventricular wave.

When auricular flutter is present with a regular rhythm and a ventricular rate of 120 to 180 beats per minute it must be differentiated from sinus tachycardia and auricular paroxysmal tachycardia. In auricular flutter the ventricular rate remains constant within narrow limits and is not affected appreciably by exercise. This is in contrast to the variability of the rate in sinus tachycardia but does not aid in distinguishing the condition from auricular paroxysmal tachycardia. In auricular flutter pressure on the right or left carotid sinus may cause transient slowing of the heart or abrupt standstill of short duration followed by resumption of the original rate. The first of these responses may also be obtained in patients with sinus tachycardia but the second does not occur. In auricular paroxysmal tachycardia, pressure upon the carotid sinus either causes an abrupt reversion to normal sinus rhythm or has no effect at all.

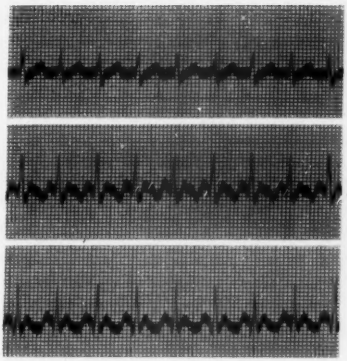


FIG. 7. Auricular flutter with 2:1 block. The ventricles respond to every second flutter wave. The flutter waves are triangular in shape, perfectly regular, and not separated by an isoelectric interval.

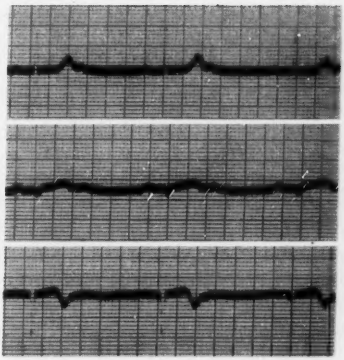


FIG. 8. 2:1 auriculoventricular block. Every second auricular impulse is blocked at the A-V node, and the corresponding ventricular beat fails to occur.

When the degree of auriculoventricular block in auricular flutter is variable, the ventricular rhythm is irregular and may suggest auricular fibrillation. Careful auscultation usually enables one to detect an underlying dominant rhythm, however, and this distinguishes the condition from auricular fibrillation. Furthermore, pressure upon the carotid sinus in auricular fibrillation has neither of the effects upon the rate of the ventricles which occur in auricular flutter.

Although the administration of quinidine sulfate may convert auricular flutter to sinus rhythm, the treatment of choice consists of rapid digitalization. In successful cases, digitalis converts auricular flutter to auricular fibrillation,

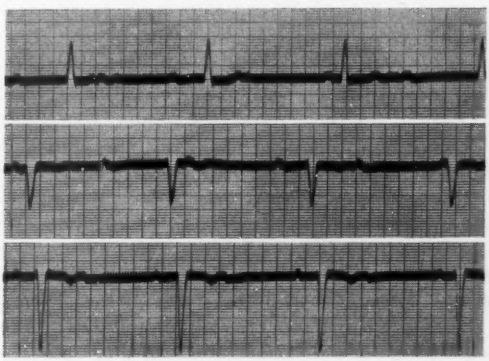


FIG. 9. Complete auriculoventricular block. All auricular impulses are blocked at the A-V node, and the activity of the ventricles is governed by an ectopic focus in the bundle of His.

and discontinuance of the drug may then be followed by spontaneous resumption of normal rhythm. If the flutter persists, digitalis is continued in the amount required to maintain sufficient auriculoventricular block to result in a ventricular rate of 100 beats per minute or less.

Auriculoventricular Block

Auriculoventricular block may be of any degree from simple lengthening of auriculoventricular conduction time to complete dissociation of the auricles and ventricles. Prolonged conduction between the auricles and ventricles, termed first degree auriculoventricular block, can be recognized with precision only by means of the electrocardiogram. The higher grades of block, namely second degree block with occasional or regularly recurring dropped beats and complete auriculoventricular dissociation, often can be diagnosed from the findings on auscultation of the heart. When there are occasional dropped beats, one must be sure that an early and faint premature beat is not being overlooked. In 2:1 block (fig. 8), the ventricular rate is slow, usually in the neighborhood of 40 per minute, and an extra heart sound may be audible shortly after the second sound. This results from those auricular contractions which are not followed by a ventricular response. In complete auriculoventricular block (fig. 9), the ventricular rate is usually less than 40 per minute. The extra sounds due to the auricular beats can be detected at times, and there usually is an occasional accentuation of the first sound at the apex due to the chance occurrence of practically simultaneous contraction of the dissociated auricles and ventricles.

Complete auriculoventricular block and second degree block with a slow ventricular rate must be distinguished from sinus bradycardia. This may not be possible by physical examination unless the auscultatory signs mentioned are present or unless one can detect extra auricular waves on inspection of the jugular pulse. Diagnostic help may be obtained, however, from the fact that in complete block exercise causes little or no change in the ventricular rate, but in sinus bradycardia a distinct increase in rate usually results.

In patients who have myocardial insufficiency, the presence of auriculoventricular block does not contraindicate the administration of digitalis. When the block is of first or second degree, digitalization should be accomplished gradually, and the effect of the drug should be observed by daily electrocardiograms. If the degree of block increases, it may be advisable to be satisfied with less than complete digitalization.

The higher grades of auriculoventricular block, and particularly complete auriculoventricular dissociation, may be complicated by the Adams-Stokes syndrome due to sudden slowing of the ventricular rate, temporary standstill of the ventricles, or the occurrence of ventricular paroxysmal tachycardia. The attacks are characterized by faintness, dizziness, syncope, or convulsions, depending on the extent to which cerebral circulation is diminished. Adams-Stokes seizures are rare, but individuals in whom they occur are liable to have repeated attacks. The actual seizures usually are of such short duration that they do not require treatment, but in rare instances ventricular standstill is of

sufficient duration to threaten life, and the intracardiac injection of epinephrine hydrochloride, 0.5 to 1.0 cc. of 1:1000 solution, is indicated. The most effective drugs for preventing recurrent attacks due to sudden ventricular slowing or ventricular asystole are epinephrine hydrochloride, 0.3 to 1.0 cc. of the 1:1000 solution, subcutaneously or intramuscularly every two to four hours, ephedrine sulfate by mouth in doses of 24 to 30 mg. every four to six hours, and paredrine by mouth in doses of 40 to 60 mg. three times a day.

Summary

The clinical features and treatment of the various types of cardiac arrhythmia have been discussed. The two most valuable drugs in treatment are digitalis and quinidine sulfate and the indications for their administration have been reviewed.

The clinical characteristics of the disturbances of cardiac rhythm have been so well established that is possible to recognize most of them without mechanical aid. Premature beats, auricular paroxysmal tachycardia, ventricular paroxysmal tachycardia, auricular fibrillation, auricular flutter, and high grade or complete auriculoventricular block usually can be detected by careful physical examination alone. Electrocardiographic corroboration of the diagnosis is always desirable, but the electrocardiogram is of much greater value today in the detection of heart muscle damage and disturbances of intraventricular conduction than in the differentiation of the cardiac arrhythmias.

References

1. Weisberger, A. S., and Feil, H.: Lanatoside C in treatment of persistent paroxysmal auricular tachycardia. Am. Heart J. **34**:871-877 (Dec.) 1947.
2. Youmans, W. B., Goodman, M. J., and Gould, J.: Neosynephrine in treatment of paroxysmal supraventricular tachycardia. Am. Heart J. **37**:359-373 (March) 1949.
3. Levine, S. A.: Treatment of acute coronary thrombosis. J.A.M.A. **99**:1737-1740 (Nov.) 19, 1932.
4. Gold, H. et al: Management of disorders of cardiac rhythm. Am. J. Med. **5**:110-125 (July) 1948

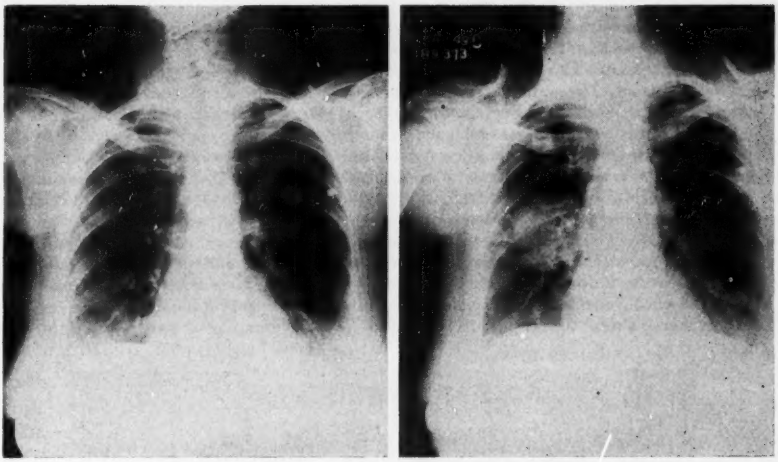
SOLITARY LUNG METASTASIS

DONALD B. EFFLER, M.D.
Department of Thoracic Surgery

IN 1938 Barney and Churchill[1] reported the successful treatment of a patient who had a primary tumor of the kidney and an accompanying metastatic lesion in the right lung. This patient is believed to be the first successfully treated by surgical removal of the primary neoplasm and subsequent excision of the metastatic lung tumor. During the next nine years there were five reports of similar case histories in which the surgeon had deliberately undertaken to remove a pulmonary metastasis after resection of a primary neoplasm elsewhere. It has been only in recent years, however, that the philosophy of treatment of a solitary pulmonary metastasis has attracted widespread interest and promises to become an accepted surgical procedure. The most comprehensive report that has appeared in the literature to date is that of Alexander[2] who collected approximately 19 unreported case histories which could be classified in this category. Blades and Effler[3] in February, 1948, reported 9 cases of solitary metastasis that had been resected following the removal of the primary tumor. Considerable discussion on this subject was carried out at the meeting of the American Association of Thoracic Surgery in 1949. A complete report of the transactions will be published by that organization. The impression was gained, however, that the majority of thoracic surgeons today accept the philosophy of resection of a solitary lung metastasis in selected cases.

It has long been recognized that primary neoplasms frequently undergo a distinctive life cycle. Certain tumors have a predilection for early widespread metastases, whereas another type may have a late spread with comparatively few metastatic lesions. Many tumors will have a predilection for a metastasis to certain viscera while others will more commonly invade by direct extension only into the adjacent tissues. From the information that we have accumulated in the treatment of solitary lung metastasis, it appears that certain tumors are capable of attaining large size without acquiring the increasing tendency to metastasis. Renal and uterine adenocarcinomata have frequently demonstrated this unusual property. Likewise, a single metastasis may appear simultaneously with the discovery of the primary tumor or many years after its removal. Whereas most neoplasms pursue a pattern characteristic of their cell type, each is still capable of a bizarre individual manifestation.

Surgical resection of a solitary lung metastasis can scarcely be classified as a basic principle of surgery. In the author's opinion, it is a matter of personal philosophy and must remain as such until there have been sufficient cases and time to arrive at basic conclusions. It has been rather common practice in the profession at large to accept the premise that the presence of a metastasis renders prognosis hopeless. There is certainly evidence at this time to indicate that this conclusion is not always justifiable. When a primary



(*a*) (*b*)

FIG. 1. (a) Routine roentgenogram of chest made at time of first admission to hospital. (b) Chest film three years later demonstrating large intrapulmonary solitary metastasis.

neoplasm is amenable to resection and no metastases are present, there is no question that it should be removed for the ultimate safety of the patient. Postoperative observation of such cases will occasionally reveal the unexpected appearance of a solitary metastasis in the pulmonary parenchyma. Frequently this will be detected on the progress roentgenogram of the chest and will be manifest before the onset of symptoms. Unless the lesion is amenable to roentgen therapy or can be successfully resected, the ultimate prognosis becomes hopeless and the patient will eventually die of this primary neoplasm. If there are no contraindications to surgery and careful examination reveals no other metastases, it would seem that the patient has a good deal to gain and very little to lose by resection of the metastatic pulmonary lesion. It goes without saying that the patient or his family should be confronted with the available facts and acquainted with all the risks involved. Although most of the patients operated upon for a single metastasis will eventually have an unfavorable outcome, the small number who do obtain cure and the larger percentage who receive prolongation of life are ample justifications of this procedure.

Case Report

A 69-year-old white housewife reported at the Cleveland Clinic on July 23, 1946, because of an unusual vaginal discharge that appeared in April of that same year. Menopause had occurred twenty years prior to the occurrence of the sanguineous vaginal discharge. In addition to this complaint, the patient had been a known diabetic for three years and had been controlled by dietary measures alone. Physical examination at this time was not remarkable and on July 25, 1946, cervical dilation was carried out and material obtained by curettage of the uterus contained microscopic evidence of a well differentiated adeno-

carcinoma. On August 24, 1946 the patient was operated upon by Dr. George Crile, Jr., and a panhysterectomy performed. The subsequent pathologic report stated that there was a well differentiated adenocarcinoma of the fundus of the uterus with moderate extension into the myometrium. The fallopian tubes and ovaries were entirely negative from the standpoint of neoplasm. The patient made an uneventful postoperative recovery and was discharged from the hospital on September 3, 1946. A routine radiographic examination of the chest prior to this operation was reported as essentially negative (fig. 1a).

The patient returned to the Cleveland Clinic seven months later for re-examination. At this time she was free of all symptoms and manifested a weight gain of approximately twelve pounds since operation. Examination on November 23, 1948, did not reveal evidence of recurrence or metastatic neoplasm.

On June 4, 1949, the patient returned complaining of a severe cough which had been present for approximately three months. According to the patient, the cough was not productive except for an occasional bit of phlegm which she felt arose from the pharynx rather than the tracheobronchial tree. The significant findings on examination at this time revealed a weight loss of almost fifteen pounds and radiographic evidence of a mass in the right hilar

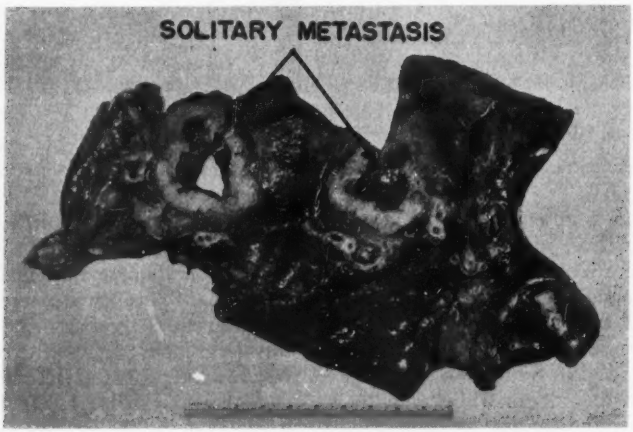


FIG. 2. Resected right lung which has been transected to demonstrate large cavitated solitary lung metastasis. Microscopic studies confirm clinical impression of adenocarcinoma from the uterus.

region. The remainder of her studies were essentially normal and the patient was advised to be admitted to the hospital for further study and treatment. The patient was hospitalized on June 22, 1949, and a careful physical examination failed to reveal any other evidence of neoplasm. Radiographic examination of the chest demonstrated an irregular globular mass in the right mid lung field which was interpreted by the roentgenologist as neoplasm, either a bronchogenic carcinoma or a solitary metastasis (fig. 1b).

On June 23, 1949 a right thoracotomy was performed and the lung carefully examined. A mass, roughly the size and shape of a lemon, was found in the right hilar region that seemed to involve both the upper and middle lobes. It appeared to be reasonably well encapsulated and an attempt was made to biopsy its wall. When a small portion of the capsule was excised, the mass was found to contain a liquid necrotic material that was amenable to aspiration, leaving a large cavity. Frozen section examination revealed it to be a metastatic adenocarcinoma that had undergone central cavitation and appeared to be metastatic from either

uterus or bowel. Due to the location of the tumor at the hilum, lobectomy was not feasible so a right total pneumonectomy was carried out. This procedure was accomplished without difficulty and no other evidence of metastases was demonstrated. Recovery from this operation was surprisingly uneventful and the patient was ambulatory on the third postoperative day. The diabetic element was easily controlled by a simple dietary regime based on 1600 calories. The patient was discharged from the hospital to home convalescence on July 2, 1949.

The final pathologic report revealed a neoplasm located between the bifurcation of the right mainstem bronchus. The lesion was 4 cm. in diameter with a necrotic cystic central portion and it appeared to be well circumscribed. The microscopic diagnosis was adenocarcinoma compatible with secondary adenocarcinoma of uterine origin. The neoplasm was well differentiated with extensive necrosis and no evidence of secondary lymph node involvement in the seven glands that were examined (fig. 2).

Comment

The surgical treatment of solitary lung metastasis is indicated in selected cases. Long and careful follow-up examinations are necessary to arrive at conclusions as to the degree of cure or palliation that will be obtained. A solitary metastasis may be present at the time the primary neoplasm is first detected or, as in the reported case it may appear years after the removal of the primary tumor. Brezina and Lindskog[4] report a pneumonectomy in 1943 for a tumor that proved to be a metastatic adenocarcinoma of uterine origin in a patient who had undergone hysterectomy thirteen years prior to that time. With the knowledge that metastases may appear well beyond the accepted five-year period, the surgeon who will undertake to excise apparent solitary metastasis must in turn be extremely cautious before proclaiming a cure. A truer valuation of this surgical philosophy will necessitate the study of a large number of cases and a long period of postoperative observation.

References

1. Barney, J. D. and Churchill, E. D.: Adenocarcinoma of kidney with metastasis to lung. Tr. Am. A. Genito-Urin. Surgeons **31**:71-79, 1938.
2. Alexander, J. and Haight, C.: Pulmonary resection for solitary metastatic sarcomas and carcinomas. Surg., Gynec., and Obst. **85**:129-146 (Aug.) 1947.
3. Effler, D. B. and Blades, B.: Surgical treatment of solitary lung metastasis. J. Thorac. Surg. **17**:27-37 (Feb.) 1948.
4. Brezina, P. S. and Lindskog, G. E.: Total pneumonectomy for metastatic uterine carcinoma. J. Thorac. Surg. **12**:728-733 (Dec.) 1943.

COUGHING AND UNCONSCIOUSNESS

The So-Called Laryngeal Vertigo

J. P. PROUDFIT, M.D.* and LOUIS J. KARNOSH, M.D.
Department of Neuropsychiatry

LARYNGEAL VERTIGO is a dramatic syndrome, first described by Charcot[1] in 1876, in which coughing produces unconsciousness with or without convulsions. At times only giddiness follows the cough which is attributed to spasm of the larynx with closure of the glottis. The cough is reported to be distinctive in character and is usually preceded by a tickling sensation in the throat. In some cases the cough is mild. The syndrome occurs most commonly in middle aged men. They are described as being plethoric, emphysematous, or having a tendency to hypertension. There is a frequent association with laryngitis or bronchitis. Many physicians are unaware of the existence of such a condition.

The syndrome is not rare. Whitty[2] reviewed the literature in 1943 and reported approximately 85 cases. Many cases have not been reported because as Rook[3] says, "They do not get past the general practitioner who adopts a very reasonable 'wait and see' attitude," the attack often not being repeated. In the past year one of us, on a general diagnostic service, has seen two examples of this syndrome. Adams[4] reports that 3 such cases were referred to him by a single physician within a period of a few months.

Case Reports

Case 1. A 43-year-old coal miner was seen at the Cleveland Clinic February 19, 1948. He complained that he had "blacked out" after coughing on 8 occasions during the past four years. He coughed violently until he "got blue in the face" and fell unconscious to the floor. He hurt himself in several of these falls. As he coughed he bent forward slightly and awakened as he hit the floor. There was never any convulsive movement or incontinence. After the spell he felt weak and nervous. He believed that he could abort an attack by sitting down and "supporting" himself. Six or 7 times a day he would think he was about to have an attack which did not materialize; for the past few weeks he had been slightly dizzy all the time. There had never been any true vertigo, tinnitus, or deafness.

Frequently small furuncles had developed in his ear canals off and on over the past six or seven years. He had a dry throat at times but no hoarseness and a non-productive cough. There was a mild constant ache in the mid-chest anteriorly, unrelated to exertion. He said that he wheezed in cold, damp weather and there were times at night when he had to sit up to get his breath. He denied exertional dyspnea. He had had considerable gaseous distress with a smothery feeling in the epigastrium occurring about fifteen minutes after meals but obtained some relief with soda. He drank about 1 quart of whiskey per month. He smoked a package of cigarettes a day.

Thirteen siblings were living and well. There was no history of epilepsy or allergic disease in the family. Pleurisy followed a herniorrhaphy in 1927. A urethral discharge was present in 1930, 1939, and 1943. Pneumonia occurred in 1904 and 1918.

**Former Fellow in Medicine, Cleveland Clinic. Now practicing in Washington, Pennsylvania.*

The patient was a large, obese white man of good color. He was 69½ inches tall and weighed 194 pounds. His pulse rate was 92 per minute. The blood pressure was 140/92. The ear canals were normal, as were the drums. The larynx appeared normal except for slight asymmetry of the epiglottis. The chest auscultation revealed persistent sibilant expiratory rhonchi in the right lower lobe. The heart was normal. Carotid pressure produced no symptoms. The finger nails were beaked but there was no clubbing. The reflexes were physiologic.

The vital capacity measured 3000 cc. (normal, 5200 cc.). The chest x-ray showed no evidence of active pulmonary disease. The electrocardiogram, urinalysis, and hemogram were normal. The sedimentation rate was 0.4 (normal up to 0.45) by the Ernstene-Rourke method. The fasting blood sugar was 108 mg. per cent. The Wassermann and Kahn tests were negative.

Case 2. A 57-year-old retail clothier of German-Jewish extraction was seen in the Clinic October 22, 1948. He gave a history of having become unconscious on 3 occasions following violent coughing. These attacks had occurred in April, 1947 and on October 8 and October 19, 1948. On the latter occasion he had fallen unconscious through a plate-glass window. There was no warning. The cough had a peculiar quality. It occurred in a severe paroxysm, "shutting off his wind." He then fell unconscious and remained so for two or three minutes without any jerking or incontinence. For five or ten minutes after recovering consciousness he felt slightly dizzy and confused. At times he had a sensation that there was something in his throat. He coughed a great deal in the mornings without dizziness or loss of consciousness. At times he even coughed so that he would vomit mucus.

He denied any ear symptoms. He had mild leg cramping at night only. He admitted drinking 1 to 4 shots of whisky daily. He smoked a pipe only. He denied hoarseness. He had influenza in 1918 and gonorrhea in 1922. There was no history of epilepsy or convulsions, nor was there a history of epilepsy or mental disease in his family.

The patient was an obese white man with a sallow complexion. The height was 68 inches. He weighed 212 pounds. The pulse rate was 82 per minute. The blood pressure was 138/92. The ears were normal with the canals almost insensitive to manipulation. The vocal cords were thick and injected. The heart and lungs were normal. The reflexes were physiologic. Hyperventilation produced no symptoms. Carotid sinus pressure on one side and then the other produced no symptoms. Simultaneous pressure over both carotid sinuses precipitated unconsciousness for five seconds or so, accompanied by generalized clonic convulsive movements.

X-ray examination of the chest showed a haziness at the right base but was interpreted by the radiologist as "probably negative." The blood count was normal as was the Kahn and Wassermann tests. The electroencephalogram was normal. The report stated that there were a few irregular waves from the left parietal leads which appeared to be artifacts.

Case 3. A 48-year-old salesman first visited the clinic on February 16, 1949. He gave a history of having coughed since 1937. Since 1943, he had experienced asthmatic attacks. The cough and the asthma had become more severe since 1947. In the year before coming to the clinic he had increasingly frequent blackouts with severe coughing paroxysms. Following coughing he suddenly slumped to the floor unconscious and in a matter of seconds regained consciousness. There were no convulsions nor incontinence. The attacks had varied in frequency from 3 or 4 a day to only 1 or 2 per week.

He claimed moderate dyspnea on exertion with some tightness in his chest. He drank little alcohol but smoked a package of cigarettes per day.

There was no family history of epilepsy or mental disease. His father died of tuberculosis and diabetes as did an aunt and uncle. He had malaria as a child. In 1918 he had influenzal pneumonia and in 1921 smallpox. He acquired gonorrhea in 1921. He had painless jaundice for three days in 1925, and in 1938 a kidney stone had been passed.

His height was 68 inches he weighed 220 pounds and his blood pressure was 126/74. There was vitiligo of the hands and penis. The right ear canal contained a large wax plug. The chest was somewhat barrel-shaped. Auscultation disclosed an occasional expiratory wheeze. The heart and reflexes were normal. There was a recurrent left inguinal hernia.

The urinalysis was normal and the hemoglobin 14 Gm. The leukocytes numbered 10,500 per cu. mm. with 69 neutrophils, 6 eosinophils, 6 monocytes, and 19 lymphocytes. A blood sugar count was normal while the Wassermann and Kahn tests were negative. Chest x-ray showed prominent lung markings but was interpreted as being within normal limits

Comment

Obesity characterized each of the 3 reported cases. The patients were 20, 38, and 42 per cent above their standard weights. There was little tendency to hypertension. In case 1 the blood pressure measured 140/92, the highest recorded in the 3 cases. None gave any personal or family history of epilepsy. All said that violent coughing precipitated the attacks. True convulsions occurred in none nor did any give a history of laryngitis. There were minor laryngeal abnormalities noted in cases 1 and 2. Case 1 showed slight asymmetry of the epiglottis, and case 2 showed thickening and injection of the vocal cords. The larynx of case 3 was not examined. An attempt to cause unconsciousness by encouraging voluntary coughing in cases 1 and 2 produced no symptoms. The chest x-ray in each case was normal. Only case 2 had an electroencephalogram; it was normal. Unilateral carotid sinus pressure produced no symptoms in the 2 cases tested. In one of these, case 2, simultaneous pressure over both carotid sinuses caused unconsciousness with generalized convulsive movements. Attacks produced in this case by coughing were unaccompanied by convulsions according to the history. The significance of symptoms brought about by bilateral carotid sinus pressure is open to question. Authorities state that bilateral pressure should never be employed.[5,6]

Etiology

The etiology of laryngeal vertigo is subject to considerable debate. Laryngeal vertigo, the name most commonly used in the literature, is a misnomer because practically none of the patients had any true vertigo. That the syndrome is laryngeal in origin is indicated by the tickling in the throat which precedes the coughing. Jackson and Jackson[7] state that the appearance of the larynx during the attack is that of glottis and sphincter closure. The etiology is generally discussed under 3 headings: (1) a reflex phenomenon, (2) a laryngeal epilepsy, and (3) cardiovascular causes.

Among the reflex causes mentioned is the carotid sinus reflex. It seems unlikely that this plays much part. Whitty[2] points out that Ferris[8] makes no mention of cough in their detailed analysis of carotid sinus syncope. Sigler[6] in a recent report on 970 cases tested and found to have hypersensitive carotid sinus reflex mentions cough and unconsciousness in none of his cases. He lists 101 symptom complexes resulting from carotid pressure. Cough occurred in 6.25 per cent of the cases. In practically all of the reported cases of laryngeal vertigo pressure over the carotid sinuses has failed to produce symptoms. In one of our cases simultaneous pressure over both carotid sinuses did produce unconsciousness but those who have written most on the carotid response state that bilateral pressure should never be employed. In certain individuals such

a procedure will produce unconsciousness simply by shutting off enough of the brain's blood supply. Thus in our case it seems unlikely that the unconsciousness produced was a result of carotid sinus reflex.

The syndrome could be due to a direct reflex from the larynx via the laryngeal nerves. Movement of the larynx, as in talking, has been reported to precipitate syncope in sensitive subjects.[9] This would coincide with the increased association with laryngitis or bronchitis. Ferris[8] mentions briefly that he has seen cardiac syncope in which the reflex originated in the larynx.

Syncope could be caused by irritation of the bronchi with cardiac arrest. Weiss[6] points out that Sunder-Plassman has demonstrated the existence of sensory nerve endings, similar to those in the carotid sinus, in the intra-pulmonary portions of the bronchi and the muscularis mucosa. Stimulation of these results in cardiac inhibition. Reflex syncope could likewise be mediated via the aortic or cardiac depressor nerve from stimulation of its receptors in the pulmonary vessels.

Lilly[10] reports a case of Arnold's nerve reflex cough syndrome in which stimulation of the posterior and inferior portions of the auditory canal reproduced the symptoms. The patient had experienced unconsciousness after coughing.

Wilson [11] raised the question of an unconsidered laryngeal or respiratory reflex associated with coughing, laughing, excitement, and in his case, swallowing. He regarded laryngeal vertigo and cataplexy as related clinical entities. He presupposed a definite individual susceptibility.

Whitty[2] presents the evidence in favor of epilepsy as the basis for this syndrome. He concludes that the majority are primarily neurogenic: either a true reflex laryngeal epilepsy, an epilepsy with a laryngeal aura, or venous congestion from violent coughing in a patient with a cerebral cortex predisposed to epilepsy. In the first, the cough would be the trigger mechanism setting off the attack. Epilepsy seems unlikely in view of the normal electroencephalographs in these cases. In only one reported case (Whitty's third case) was there a record suggestive of epilepsy. Whitty believed that he ruled out cerebral congestion as a cause when he failed to reproduce the symptoms by inflating a sphygmomanometer cuff placed about the patient's neck.

The cough reflex is most commonly initiated by stimulation of the afferent nerve endings in the region of the tracheal bifurcation or in the laryngeal mucosa. During forced expiratory effort with the glottis closed considerable pressure is developed within the lung. This results in decreased venous return and poor oxygenation as indicated by the familiar expression, "coughed till he got blue in the face." Cerebral congestion results. Rook[3] points out that blowing through a tube in an effort to maintain a column of mercury at a height of 40 mm. will result in unconsciousness in certain individuals. Negative acceleration of human subjects on a centrifuge, with the blood rushing to the head, has not produced unconsciousness. However, there is no noticeable increase in intrathoracic pressure in such experiments as there is with coughing. Pertussis coughing may produce cerebral hemorrhage. Rook[3] believed that this evidence favored cerebral congestion with anoxia and increased intracranial

pressure as the cause of laryngeal vertigo. It may well be that two or more factors must be present to produce an attack of unconsciousness. It is not surprising, therefore, that attempts to reproduce the symptoms by voluntary coughing or by such methods as attempting to obstruct the venous return from the head do not meet with success.

Weiss,[5] in discussing syncope, says that it can result from increased intrapulmonary pressure, as in the Valsalva experiment. The act of coughing, consisting of a short inspiration followed by closure of the glottis and a forcible expiration with the production of considerable increase in intra-pulmonary pressure, is not unlike the Valsalva effort.

Increased intraspinal pressure and engorgement of the intracranial vessels is a cause of syncope particularly in stooping or lowering the head.[5] Coughing is generally performed in just such a position. Coughing causes increased cerebrospinal pressure and cerebral congestion.

Treatment of laryngeal vertigo is entirely symptomatic. Phenobarbital is probably of value but only as a sedative and not as an anticonvulsant.

It seems well to conclude that the etiology of laryngeal syncope is complex. Factors of importance in its production include a direct reflex originating in the larynx, reflexes arising in sensory end-organs within the bronchi, increased intrapulmonary pressure with anoxia (Valsalva), and increased intracranial pressure and cerebral engorgement. There seems little reason to implicate epilepsy, cataplexy, or a carotid sinus reflex for which there must be an individual susceptibility.

References

1. Charcot, J. M., cited by Rook, A. F.[3]
2. Whitty, C. W. M.: On so-called "laryngeal epilepsy." Brain **66**:43-54 (March) 1943.
3. Rook, A. F.: Coughing and unconsciousness; so-called laryngeal epilepsy. Brain **69**:138-148 (June) 1946.
4. Adams, D. K.: Clinical incidence of laryngeal vertigo. Glasgow M.J. **125**:278-280 (June) 1936.
5. Gowers, cited by Weiss, S.: Syncope and related syndromes. Oxford System of Medicine **2**: part 1, 250 (9-66), 1935.
6. Sigler, L. H.: Subjective manifestations of hyperactive carotid sinus reflex. Ann. Int. Med. **29**:687-697 (Oct. 4) 1948.
7. Jackson, C., and Jackson, C. L.: Diseases and Injuries of the Larynx, ed. 2 (New York: The Macmillan Company, 1947).
8. Ferris, E. B., Jr.: Fainting: Diagnosis and treatment. J. Med. **20**:342-344 (Oct.) 1939.
9. Penfield, W., and McEachern, D. S.: Some observations upon carotid sinus pressor reflexes based on surgical denervation in 50 patients. Tr. Am. Neurol. A. **71**:72-73, 1946.
10. Little, H. I., and Thornell, W. C.: Arnold's nerve reflex cough syndrome. Ann. Otol., Rhin., and Laryng. **53**:770-773 (Dec.) 1944.
11. Wilson, J. G.: Laryngeal vertigo and its relation to cataplexy. Tr. Am. Laryng. A. **53**:105-122, 1931.

SPINAL EXTRADURAL GRANULOMAS

JOHN R. HANNAN, M.D.* and RICHARD L. MASON, M.D.
Department of Roentgenology

CHRONIC epidural inflammatory tumors are uncommon. Browder and Meyers,[1] in a review of the literature from 1820 to 1937 found 52 cases. In a survey of all epidural compressive lesions at the Hospital of the University of Pennsylvania from 1934 to 1944, Shenkin, Horn and Grant[2] discovered three lesions of this type. There is no doubt that some cases have been unrecognized or unreported. The literature on epidural granulomas during the past ten years has been sparse and the roentgenologic features have not been stressed. We are reporting observations in two chronic extradural granulomas in order to emphasize the roentgenologic manifestations.

Case Reports

Case 1. A 42-year-old man entered the Cleveland Clinic on May 10, 1945 complaining of rheumatism of two years' duration. His pain began in the left hip and radiated down his left leg to the ankle. Although constant, it was intensified by coughing, sneezing and laughing. Physical examination demonstrated restriction of motion in the back. Routine laboratory studies were normal. A dental examination disclosed no focus of infection. A roentgenographic examination of the lumbar spine indicated moderate osteoarthritis. Fibrositis, rheumatoid arthritis of the spine and disk herniation were tentatively considered as possible diagnoses and thiamin chloride was advised as well as a firm mattress and a course of diathermy and massage. The patient was asked to return in two months if there was no improvement in his condition.

He returned on November 16, 1945 unimproved. A neurologic examination revealed tenderness over L-1. On lumbar puncture between L-2 and L-3 xanthochromic fluid was recovered. Dynamic tests demonstrated partial subarachnoid block. The cerebrospinal fluid contained 200 cells with 90 per cent lymphocytes and the protein was 850 mg. per cent. Progress x-ray films of the lumbar spine showed an area of increased density in the left pedicle and lamina of L-2. A cisternal pantopaque myelogram revealed a partial block at L-2 with a lateral defect in the opaque column, and in addition demonstrated the sclerosis about the pedicle in L-2 (fig. 1). The first preoperative clinical impression was extradural abscess and the second was cord tumor.

On November 21, 1945 a laminectomy was performed under pentothal anesthesia. The lamina of L-2 to the left of the midline was hard and thickened. An extradural grayish hard tumor was found attached to the ligamenta flava. The mass extended along the left side of the spinal canal and compressed underlying nerve roots. The tumor was dissected from the dura with difficulty and the dura was thickened and adherent to cauda equina. When the dura was opened, the operator observed that some of the nerves of the cauda were adherent to each other. The entire mass could not be removed and the dura was left open.

The microscopic examination showed dense, partly hyalinized fibrous connective tissue, in which were present many miliary and larger foci composed of large mononuclear cells. Between these small nodules there was diffuse infiltration with lymphocytes and plasma cells, and occasional polymorphonuclear leukocytes. The diagnosis was, "acute and chronic granulomatous inflammatory tissue, non-specific."

---

*Now of 10515 Carnegie Avenue.

FIG. 1. Case 1. Extradural granuloma. Cisternal myelogram. Partial block opaque media upper border L-2. (a) Lateral defect in opaque column; (b) bone sclerosis in pedicle and lamina of L-2.

FIG. 2. Case 2. Extradural granuloma. Cisternal myelogram. Partial obstruction upper border of D-7 with central linear defect and lateral displacement of lipiodol.

The patient was given penicillin and his course was uneventful until the twelfth postoperative day when a purulent discharge emitted from the incision and staphylococcus aureus was cultured. This was controlled by irrigations and additional penicillin. From December 15 to 22, 1945, 2200 r. were delivered to the skin over the operative site (200 KV, H.V.L. 1.4 mm. cu., 10 by 20 cm. field, 50 cm. F.S.D.). The patient was discharged on December 15, 1945.

On return visit in January, 1947 he appeared improved, had gained 15 pounds and was working steadily. However, in December, 1947 he returned complaining of a tender, red swelling about 4 cm. in diameter over his right sacroiliac region. Incision and drainage of this abscess were performed on January 3, 1948 and a culture showed staphylococcus albus.

On November 1, 1948 the patient again returned complaining of recurrent pain in the posterior aspect of the left thigh and calf. Another course of roentgen therapy was advised. Between November 2 and November 12, 1948, 2200 r. (200 KV, H.V.L. 1.4 mm. cu. field size 10 by 20 cm., 50 cm. F.S.D.) were delivered to the skin over L-1, L-2 and L-3. The patient was much improved following this course of radiation therapy and has not returned since for observation.

Case 2. On May 12, 1941 a 31-year-old woman came to the Cleveland Clinic stating that she had been conscious of a continuous boring pain in her dorso-lumbar region since November, 1940. The pain radiated, girdle-like, around her chest. Two weeks before admission she first experienced paresthesias in her feet and noted weakness of both legs. There were no sphincter disturbances.

The patient had had syphilis in 1937 which had apparently been adequately treated over a three-year period. Her physical examination was satisfactory except for slight tenderness over D-8, D-9 and D-10. Biceps, triceps, knee and ankle jerks were hyperactive and the abdominal reflexes were absent. The Babinski sign was negative. There was hypesthesia below D-6.

Lumbar puncture between L-4 and L-5 disclosed a partial subarachnoid block. The fluid was clear and no cells were found. Spinal fluid protein was 95 mg. per cent; the Wassermann was negative; the colloidal gold curve was not abnormal. There were no visible cells. Wassermann and Kahn tests on the blood were normal. Roentgenograms of the dorsal spine showed no abnormal changes. Cisternal lipiodol myelogram revealed a partial obstruction at D-7 and a central linear defect with lateral displacement of the oil (fig. 2).

A dorsal laminectomy was done on May 15, 1941 under avertin anesthesia. A sleeve of extremely hard extradural tissue covered the dorsal aspect of the cord. The mass was centered at D-7 and measured 6 cm. in length.

Microscopic examination of the tissue showed chronic granulation tissue and many polymorphonuclear leukocytes and plasma cells. The appearance did not suggest a syphilitic lesion. A culture of the tissue demonstrated staphylococcus albus. Roentgen irradiation was started on May 21 and between May 21 and 23, 425 r. were delivered to the skin over the operative site. (200 KV, H.V.L. 1.4 mm. cu., field size 15 by 20 cm., F.S.D. 50 cm.)

On the ninth postoperative day the wound was reopened because of induration and deep suppuration. Staphylococcus aureus was cultured. Five Gm. of sulfanilamide powder was placed in the wound and a deep pack was inserted. Progress was satisfactory and the patient left the hospital on June 15, 1941. Her hypesthesia had diminished and she had fairly good use of her legs at the time of hospital discharge. She has not returned for examination but on March 14, 1949 her local physician wrote that she has continued in good health.

Discussion

Spinal extradural inflammatory lesions may be either acute epidural abscesses or chronic epidural granulomas. Usually in the acute suppurative lesion the source of infection is readily determined. In many of the chronic granulomas, as in our cases, no source of infection can be detected. It is then most difficult to differentiate clinically a nonspecific granuloma from a cord

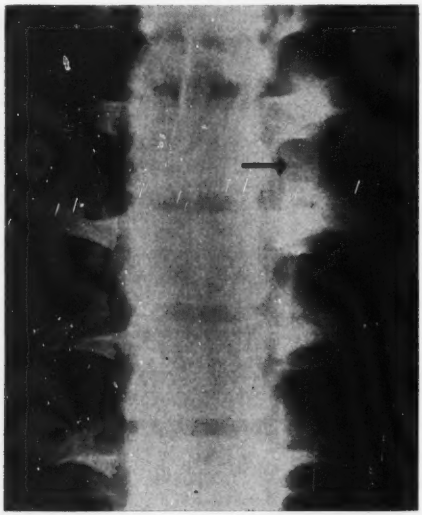


FIG. 3. Nonspecific extradural and paravertebral abscess in boy 16. Developed vague neurologic symptoms three months after acute pharyngitis. Spinal fluid protein 67 mg. per cent. 67 white blood cells in spinal fluid. Arrow indicates localized paravertebral soft tissue bulge.

FIG. 4. Extradural Hodgkin's granuloma. Partial block lower border of D-5 with lateral displacement of opaque media. Pattern somewhat similar to myelogram in case 2 (fig. 2).

tumor. All gradations between epidural abscess and granuloma are apt to occur dependent on host resistance and the type and virulence of the organism.

Both specific and nonspecific granulomas have been described. The former are usually tuberculous or syphilitic. Our first patient had a nonspecific lesion. In the case of the second patient there might be a question as to whether the granuloma was syphilitic or nonspecific in character. Because the patient had had adequate antiluetic therapy, because the Wassermann tests on the blood and spinal fluid were negative, and because the microscopic picture did not suggest a syphilitic lesion, we have also classified the granuloma found in the second patient as nonspecific.

Watts and Mixter[4] claim that extradural inflammatory lesions seldom develop primarily in the epidural space. They frequently develop by hematogenous or lymphogenous extension from a primary focus elsewhere or they may occur through direct extension from infections in contiguous structures. Browder and Meyers[1] believe that in the hematogenous type metastasis is first to a vertebra, producing vertebral osteomyelitis and the infection then extends into the epidural space. Among the reported primary foci are carbuncle, furuncle, cellulitis, dental abscess, pneumonia, osteomyelitis, perirenal abscess, otitis media, pharyngitis, tonsilitis, pyelitis and puerperal sepsis.

Dandy[3] and others have emphasized that inflammatory lesions are more frequent in the dorsal spine and that they localize posterolaterally because anteriorly the dura is adherent to the posterior longitudinal spinal ligament.

Pain is nearly always the first symptom of an epidural inflammatory lesion. The time interval from a recognized inflammatory lesion to the first neurologic sign or symptom may be several months to several years. The pain may be limited to a small area along the spine. It is often exaggerated by coughing and sneezing and by jarring movements of the spine. Not infrequently the pain is bilateral and radiates along the spinal nerves. Paralysis is slow to develop and usually incomplete.

The Queckenstedt test usually demonstrates a partial or complete subarachnoid block. The spinal fluid is often xanthochromic and spinal fluid protein is frequently elevated. The elevated spinal fluid lymphocyte count caused by granulomas may be an aid in differentiating these lesions from cord tumors.

The importance of roentgenology in the diagnosis of extradural granulomas has not been stressed. There may be no characteristic changes seen on plain roentgenograms of the spine. However, in our first case there was an area of increased density in the left pedicle and lamina of L-2. This was comparable to the bone sclerosis associated with low grade osteitis elsewhere in the skeletal system. Many would agree that this lends support to the contention of Browder and Meyers[1] that a so-called "metastatic" epidural infection is always a complication of vertebral osteomyelitis. In our case it would be difficult to prove that the vertebral osteitis preceded the epidural granuloma.

Infrequently spinal cord meningiomas produce a somewhat similar hyperostosis in the neural arch or vertebral body. An hemangioma involving a vertebral body and the meninges might be confused with a granuloma clinically,

but an hemangioma produces rather characteristic stippling and parallel striations in the vertebra.

Occasionally an extradural inflammatory lesion causes localized bulging of the paraspinal soft tissues (fig. 3). Neither of our granulomas demonstrated this finding, and we believe that it is more frequent in epidural abscesses.

When there are no localizing neurologic signs and when plain films of the spine are negative, myelography is necessary to establish the level of the lesion. If there is a complete subarachnoid block, the primary object of myelography is to establish the level of obstruction and not necessarily the character of the lesion. Consequently either a cisternal or lumbar subarachnoid injection of 1 or 2 cc. of opaque media will suffice. If there is no block, or if the subarachnoid block is not complete, it is usually better to do a lumbar myelogram using a larger amount (5 cc.) of contrast media to avoid overlooking a small lesion.

Both of our lesions were localized but not specifically diagnosed by cisternal myelograms. In the first case there was a partial block at L-2 with a defect along the left margin of the opaque column. The defect was not unlike that seen in laterally placed subdural neoplasms, but the sclerosis in the pedicle of L-2 suggested that this lesion was probably extradural. In case 2 there was partial obstruction demonstrated at D-7 by myelography. The opaque media was split into two laterally placed columns. We have seen a similar appearance in one extradural Hodgkin's granuloma (fig. 4). Further observation is required before it will be possible to evaluate the importance of a linear defect in the opaque column in the absence of widening of the cord (a sign of intramedullary lesion) in the diagnosis of extradural granulomas.

Summary

Chronic nonspecific epidural granulomas are difficult to diagnose clinically when there is no history of a previous infection. They are easily mistaken for cord tumors. If routine roentgenograms of the spine do not localize the lesion, myelograms should be done to determine the level of the granuloma.

References

1. Browder, J. and Meyers, R.: Infections of spinal epidural space; aspect of vertebral osteomyelitis. American J. Surg. 37:4-26 (July) 1937.
2. Shenkin, H. A., Horn R. C. and Grant, F. C.: Lesions of spinal epidural space producing cord compression. Arch. Surg. 51:125-146 (Oct.) 1945.
3. Dandy, W. E.: Abscesses and inflammatory tumors in spinal epidural space (so-called pachymeningitis externa). Arch. Surg. 13:477-494 (Oct.) 1926.
4. Watts, J., and Mixter, W. J.: Spinal epidural granuloma. New England J. Med. 204: 1335-1344 (June) 1931.

VESICAL NECK RESECTION FOR NEUROGENIC BLADDER

WILLIAM J. ENGEL, M.D.
Department of Urology

THE vesical dysfunction which follows injury or disease of the spinal cord or cauda equina has always presented a problem. The subject received much attention during the recent war and the many civilian accidents today which produce cord injury make it a continuing problem.

In past years the lot of the patient with a neurogenic bladder was unfortunate. If he failed to develop useful automatic control it became necessary for him to wear an undesirable rubber incontinence bag or to be given a permanent cystostomy. In the past decade following the reports of Braasch and Thompson[1] and Emmett,[2] transurethral resection of the vesical neck has been employed successfully to relieve the major annoyances of neurogenic bladder.

Certain basic facts regarding the anatomy and physiology of the bladder are important. It is composed of smooth or involuntary muscle. The so-called internal sphincter is made up of fibers of the detrusor muscle which are arranged in a circular manner around the bladder outlet. These muscles (detrusor and internal sphincter) receive their nerve supply through the pelvic nerves (parasympathetic) which arise from the second, third, and fourth sacral segments of the cord. Sensory fibers from the bladder are carried over the same nerves. Thus the pelvic nerves may be considered the nerves of micturition. The sympathetic system carries some sensory fibers for pain but the sympathetic nerves are not essential for bladder function which proceeds normally even after division of all sympathetic fibers.

The reflex arc for micturition therefore consists of sensory fibers to the sacral cord which register stretch of the bladder and motor fibers through the pelvic nerve, causing contraction of the detrusor urinae and relaxation of the internal sphincter.

The external sphincter is a striated or voluntary muscle receiving its nerve supply from the external pudendal, a somatic nerve. It is believed that the contraction of the detrusor muscle initiates a reflex which results in relaxation of the external sphincter.

There are centers in the midbrain and cerebral cortex which exert an inhibitory influence on the bladder. Thus, according to Evans,[3] bladder function is controlled at several levels. The lowest level is the bladder isolated from all nervous control. The next is sacral reflex action which persists after transection of the cord above the sacral level. Next the midbrain centers coordinate bladder activity at an unconscious level, and finally, centers in the cerebral cortex constitute the highest level of nervous control of urination.

McLellan[4] has divided neurogenic bladders into four groups.

Group I. **The uninhibited neurogenic bladder** in which there is loss of cerebral inhibition. This may occur in adult patients with enuresis and some brain tumors.

Group II. **The reflex neurogenic bladder,** sometimes referred to as the automatic bladder. This type occurs when there is cord injury above the sacral segments which may be the result of trauma or compression or severe inflammation. Micturition is reflex and may be involuntary. Bladder sensation is abolished.

Group III. **The autonomous neurogenic bladder.** This occurs when the bladder is completely isolated from its nerve supply. It is encountered in lesions of the sacral cord or cauda equina. Bladder sensation is absent.

Group IV. **The atonic neurogenic bladder.** This type results from lesions of the posterior (sensory) sacral roots or when there is interruption of the afferent pathways of the reflex arc. There is complete sensory loss. The most common example of this is the tabetic bladder although it may be seen with diabetes, pernicious anemia, and other diseases involving the sensory pathways of the cord.

Group I may be ignored in this discussion which is concerned with the use of vesical neck resection in treatment. In the other three types, certain prerequisites should exist if transurethral resection is to be considered as a method of treatment.

1. **Residual urine.** This may occur in all three types. It is usually greatest in the atonic and least in the reflex neurogenic bladder although it may exceed 200 cc. even in the latter. Obviously the presence of residual urine indicates the inability of the bladder to empty its contents, a situation which requires relief.

2. **Overflow incontinence** is frequently a result of a large residual urine and may be the patient's most troublesome complaint. Overflow incontinence must be differentiated from total incontinence and from involuntary micturition which may occur in the reflex type of neurogenic bladder. The former generally occurs during sleep or under stress and is manifest by the loss of small quantities of urine. The presence of residual urine is a requisite for diagnosis.

3. **Cystoscopic evidence of neurogenic bladder** must be present. During this examination one may determine sensory loss and whether the bladder is atonic or hypertonic. Increased trabeculation is usually a manifestation of the latter. Observation of the vesical neck establishes the presence of obstruction. The physician must decide if possible whether the lesion is neurogenic or purely obstructive. In older men in the enlarged prostate age group this is not always easy although fortunately the differentiation is not too important as the treatment is the same.

4. One must **allow sufficient time to elapse between an injury to the cord and a decision to resort to transurethral resection.** This is especially true in instances of acute trauma to the cord. Following the initial shock there may be gradual resumption of normal bladder function provided the cord injury is incomplete or due to simple compression which has received appro-

priate treatment. Vesical neck resection should be delayed until the extent of nerve injury is finally established and the presence of an appreciable amount of residual urine repeatedly demonstrated.

5. We have not employed **cystometric studies** routinely in selection of cases for transurethral resection. The procedure is not necessary in establishing a diagnosis and the other considerations are more important in selecting cases for operation.

The results of vesical neck resection for neurogenic bladder have been carefully followed in 15 cases. This is a relatively small series but covers a variety of neurologic lesions. We have not included in this group any cases in which resection was performed to relieve urinary retention with large residual urine which occasionally follows the combined abdominoperineal resection for rectal carcinoma. In my opinion many of these are true neurogenic bladders but there are so many other factors involved that it is difficult accurately to classify the cases due to nerve injury alone. All cases of this type, however, have been relieved by transurethral resection of the bladder neck.

Tabes dorsalis. Five patients with atonic neurogenic bladder resulting from tabes have been treated by bladder neck resection. All were men, the youngest 50 and the oldest 63 years old. A large quantity of residual urine was present in each case (the largest 2000 cc.) and overflow incontinence was a troublesome complaint in all but one. Two operations were required in 1 patient to achieve the desired result. In the majority of cases results were exceptionally satisfactory. Three patients consider themselves perfectly normal and in these the residual urine went from 1800 cc. to none, from 2000 cc. to 50 cc., and from 1500 cc. to 100 cc. respectively. Two failures deserve special comment. One who was unimproved following the first resection refused further operation. A second patient who had taboparesis with mental deterioration underwent progressive mental change and was eventually committed to an institution.

Spina bifida. There were 4 patients with autonomous type of neurogenic bladder associated with spina bifida. All had had previous operations for correction of meningocele. The most troublesome complaint was urinary incontinence and 1 had worn a rubber urinal for twenty years. Residual urine was present in all cases, which ranged in amount from 400 to 700 cc., and was in each instance badly infected and ammoniacal. In each of these patients single operation has been carried out. All cases are classified as improved, the conclusion based upon noticeable reduction of residual urine and the elimination of diurnal incontinence. Slight loss of urine during sound sleep may persist. The improved mental attitude of these patients is often striking and their release from a state of social ostracism is gratifying and contributes to the success of the operation.

Herniated intervertebral disk. Two patients with permanent nerve injury (cauda equina) from cord compression due to herniated disk were not relieved of their bladder difficulty following laminectomy and disk removal. One man and 1 woman constituted this group. In each case bladder drainage

by suprapubic puncture cystostomy was performed, followed after an interval by vesical neck resection. Two resections were done in the woman patient. Both were completely relieved and emptied their bladders satisfactorily following removal of the suprapubic tubes.

Spinal cord injury. Two patients had traumatic injury involving the cauda equina. In each instance an autonomous type of neurogenic bladder was present with a large residual urine. Following vesical neck resection both patients were improved with evident reduction of residual urine and satisfactory control.

Retention due to spastic external sphincter. Two cases in this series are worthy of special comment. Each had a neurogenic bladder with urinary retention and a large residual urine. All obstructing tissue was resected from the vesical neck and prostatic urethra. This required two operations in one and three in the second patient. In spite of complete resection neither patient was able to void. Careful postoperative urethrascopic examination in each patient revealed an unusually spastic external sphincter which "snapped" shut as the urethrascope was withdrawn and appeared to remain in spastic closure. This was undoubtedly the explanation of the urinary retention.

Emmett[6] called attention to a case presenting the same problem and demonstrated the spastic sphincter by means of urethrograms. His patient was not relieved by bilateral section of the pudendal nerves or by anterior rhizotomy of the sacral roots. Relief of the urinary retention finally followed complete division of the cauda equina at the level of the third lumbar vertebra.

Inasmuch as this type of surgery is formidable we conceived the possibility of relieving our patients by weakening the sphincter by sectioning part of the fibers. Accordingly, by means of a specially devised electrosurgical blade attached to the McCarthy resectoscope a superficial sphincterotomy was performed at about 5:00 o'clock on the circumference of the sphincter. The cut was made an estimated depth of one-third to one-half the thickness of the muscle.

The immediate results were encouraging. By compression of the abdominal muscles assisted by some external pressure, the patients were able to void sufficiently to discontinue catheterization and permit them to leave the hospital. A follow-up report however indicates that the late results were unsatisfactory. One patient subsequently developed recurrence of urinary obstruction and has had to resume use of intermittent self-catheterization. The other who is a paraplegic patient has not regained satisfactory urinary control. These cases indicate that at present there is no completely satisfactory treatment for urinary retention due to a spastic external sphincter.

In performing vesical neck resection for neurogenic bladder I have employed the McCarthy resectoscope. I have not found it necessary in all cases to resect the entire circumference of the vesical neck but at least the lower 180° must be carefully resected. In men with even a minor degree of prostatic hypertrophy a complete transurethral resection of the prostate should be undertaken. Multiple resections may be necessary and this is especially true in women where the dictum "too little and repeat" is better than "two much

and regret." I have never seen a vesico or urethrovaginal fistula following transurethral resection in women, but the palpable thinness of the urethrovaginal septum is a constant reminder to proceed with caution.

Summary and Conclusions

In properly selected cases vesical neck resection gives gratifying results in improving patients with neurogenic bladders. In most instances retention can be relieved, residual urine reduced or abolished and troublesome overflow incontinence relieved. Patients are made more comfortable and their care simplified. Although the patient will never have a normal bladder the operation affords the opportunity of leading a more normal existence. The favorable results obtained prove the operation of definite value in the management of patients with neurogenic vesical dysfunction.

References

1. Braasch, W. F. and Thompson, G. J.: Treatment of atonic bladder. Surg., Gynec. and Obst. **61**:379-384 (Sept.) 1935.
2. Emmett, J. L.: Urinary retention from imbalance of detrusor and vesical neck. J. Urol. **43**:692-704 (May) 1940.
3. Evans, J. P.: Physiologic basis of neurogenic bladder. J.A.M.A. **117**:1927-1930 (Dec. 6) 1941.
4. McLellan, F. C.: The Neurogenic Bladder (Springfield, Ill.: Charles C Thomas, 1939).
5. Emmett, J. L., Daut, R. V., and Dunn, J. H.: Role of external urethral sphincter in normal bladder and cord bladder. Tr. Am. A. Genito-Urin. Surgeons **39**:56-71, 1947.

ARTERIAL INFUSION

DONALD E. HALE, M.D.
Department of Anesthesiology

ARTERIAL infusion is the injection of blood, or other fluid, into an artery through a needle or cannula directed toward the heart. The fluid flows in a retrograde direction against the normal arterial current.

Apparently Langendorf,[1] in 1895, was the first to employ this method. He succeeded in re-establishing heart activity in the isolated organ using defibrinated, oxygenated blood. In 1914 Crile[2] reported the arterial injection of saline solution containing epinephrine together with artificial respiration in the resuscitation of dogs. Seeley[3] made the suggestion that the intra-arterial administration of fluids might be preferable to the intravenous route in the treatment of shock. Arterial infusion has been used many times to replace blood after the induction of controlled hypotension.[4,5,6] It has been employed with success by other workers in this country and abroad.[7,8,9,10]

The procedure is most clearly indicated for those patients who are in serious cardiovascular collapse as a result of extensive hemorrhage. Such a patient, who, when first seen, is pulseless and who has an extremely low or absent blood

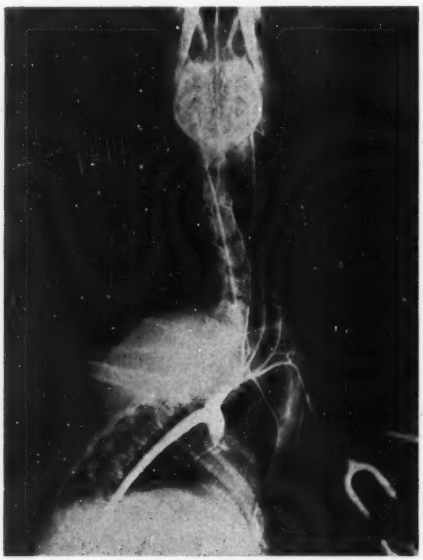


FIG. 1. X-ray of dog showing filling of coronary, carotid and vertebral arteries by injection into brachial artery.

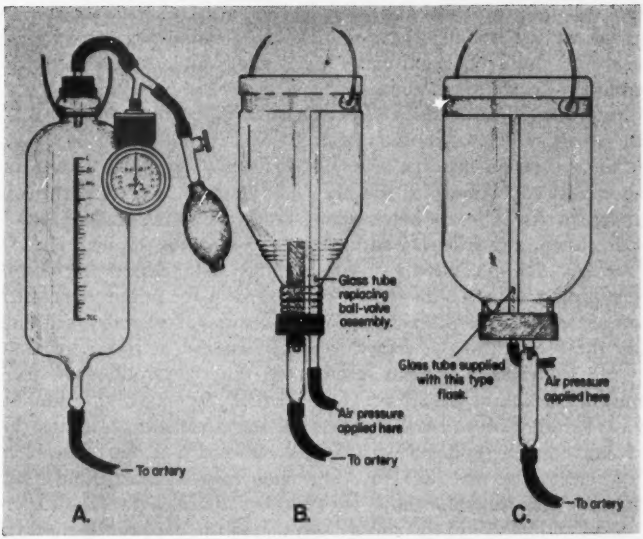


FIG. 2. (a) An open flask for arterial infusion. Measured air pressure is exerted by manometer and bulb. (b) and (c) Adaptations of commercial flasks for giving arterial infusion.

pressure needs a large volume of blood administered intravascularly in order to re-establish circulation. Even more than the need for this large volume of blood, however, is the necessity for an immediate establishment of a reasonable level of pressure in the aorta so that blood may begin to flow at once into the coronary arteries and into the arteries supplying the brain. For this purpose the artery is used simply as a channel to the aorta so that fluid introduced there, added to the fluid already present, builds up a pressure which re-establishes essential circulation. Figure 1 shows graphically that fluid injected intra-arterially can be delivered to the myocardium and brain within a few seconds. The dog shown in the x-ray had been bled until the systolic blood pressure fell to 20 mm. Hg. Thereupon 12 cc. of radio-opaque medium (diodrast 70 per cent) was injected into the left brachial artery. The x-ray taken five seconds later shows satisfactory filling of the coronary, carotid and vertebral arteries.

This represents a quite different use of intravascular injection from the ordinary intravenous administration. In the latter, the vascular system is indeed supplied with fluids, but under circumstances in which the blood stream has become severely slowed or has stopped, intravenous fluid simply dilates the relaxed veins, overfills the right chambers of the heart and pulmonary vessels without actually reaching the aorta, and consequently accomplishes nothing at all. To be sure, in those instances in which the blood stream is still moving, intravenously administered fluids do gain access to the arterial system a few seconds later and this route is therefore satisfactory. Experimental evidence has

shown that cardiac arrest in the absence of ventricular fibrillation may be corrected by the use of intra-arterial infusion of blood alone, which suggests that the method may be of great value used either alone or in conjunction with other methods of cardiac resuscitation.

The apparatus consists of a flask to hold the blood or other fluid, a length of rubber tubing sufficient to reach from the flask to the artery and a cannula or needle to be inserted into the artery. The flask is equipped with a means of supplying measured pressure to the air over the fluid. The apparatus is illustrated in figure 2a. The rubber tubing should be thick-walled and have a fairly small lumen, a satisfactory ratio being 1.5 mm. for the wall and 3.0 mm. for the lumen. The plastic disposable tubings with which the commercial flasks are supplied are not sufficiently well sealed to the adapters on either end to prevent leakage when pressures up to 300 mm. of mercury are employed for forcing the blood into the artery. On this account, it is wise to secure this tubing to the adapters by means of adhesive tape or ligatures, or to replace it with the rubber tubing described. The small mouthed blood bottle commercially available may be adapted to pressure administration of fluids. The ball valve is removed and replaced with a glass tube so that the pressure may be applied or released at will (fig. 2b). The wide mouth commercial bottle may be adapted by inserting a needle with rubber diaphragm (1/16 inch sheet rubber) into the air inlet in the rubber stopper in the neck of the flask (fig. 2c). Air is then pumped into the flask by means of a hand bulb.

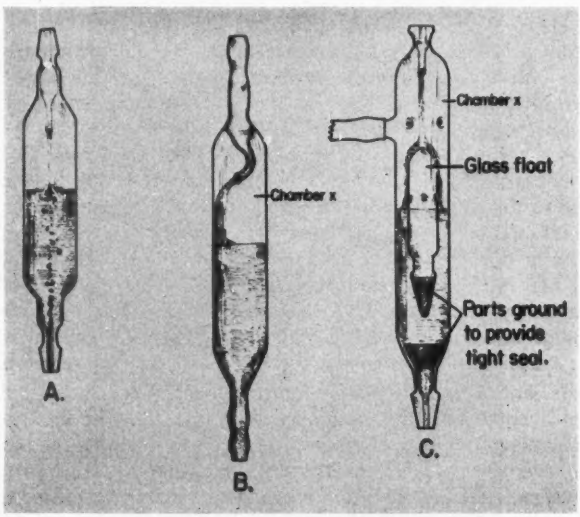


FIG. 3. (a) Murphy drip showing small air bubbles being carried into the fluid by force of stream. (b) A modification with a curved tip to deflect the fluid toward the side, avoiding formation of bubbles. (c) A modification containing glass float which prevents bubble formation and seals lower end of apparatus as last of fluid passes from it.

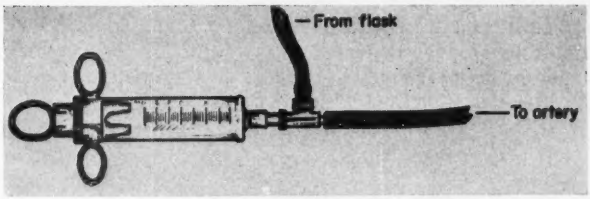


FIG. 4. Ring syringe fitted with two-way valve for giving arterial infusion.

In the earlier apparatus a Murphy drip was placed in the tubing leading from the vessel to the artery so that the movement of fluid could be observed. However, if the fluid is moving at a considerable speed into an artery in which the tension is low, small bubbles of air from the Murphy drip may be picked up by the stream and carried into the artery (fig. 3a). Although small quantities of air are ordinarily well tolerated by the body this is not true if these air emboli are carried to the aorta and gain access to either a coronary artery or a cerebral artery in the presence of extreme hypotension. Because of this the Murphy drip has been discarded or has been replaced with one with a tip bent to the side so that the fluid does not strike against the surface of the meniscus but rather trickles down the side wall (fig. 3b). A most satisfactory modification of the Murphy drip is available in England* and contains a glass float which is ground to fit the bottom of the inside of the device (fig. 3c). Bubbles cannot be carried through as their course is interrupted by the float. Furthermore, when the last of the fluid has passed into the patient's artery a massive air embolism cannot result inasmuch as the float makes a tight seal with the bottom of the Murphy drip. It should be emphasized and reiterated that massive air embolism is a complication which may accompany arterial infusion provided great care is not taken in its prevention.

Another apparatus which affords a safeguard against air embolism following arterial infusion is illustrated in figure 4. It consists of a Lok-control syringe to which is fitted a two-way valve. This allows the syringe to be filled from a reservoir containing blood and to be discharged into the tubing communicating with the artery at a rate which can be determined by the operator. It is a simple matter to replace the syringe with a new one, in the event it becomes sticky, or to place a few drops of citrate solution on the plunger. Another type of syringe may be substituted for the Lok-control, and a three-way stopcock may be used in place of the valve.

The radial artery is the one which is most often used for the injection. Some of the earliest workers used the carotid artery, and the femoral artery has proved serviceable in many cases. In a few instances, in operations during which the thoracic cavity was opened, the needle has been thrust directly into the thoracic aorta and blood under pressure administered by that route.[8] The radial artery, however, has been found to be most satisfactory because of its ready accessibility, its fairly long, straight, subcutaneous course in the wrist and

*A. Charles King, Ltd., London.

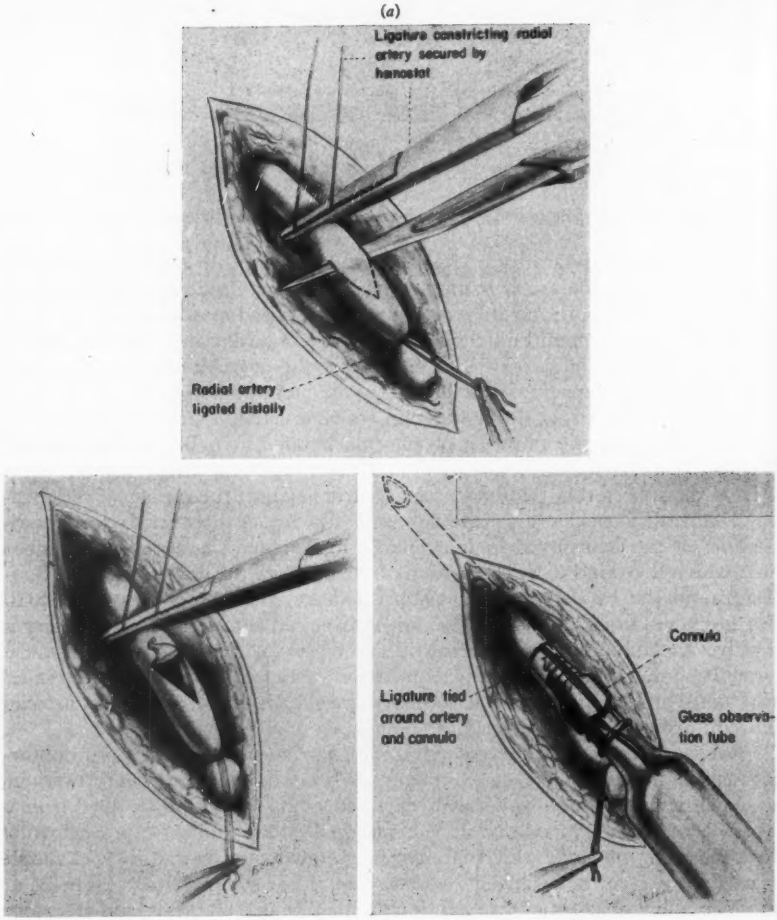


FIG. 5. (a) Artery held between ligatures while being incised. (b) Triangular opening resulting from incision. (c) Cannula secured in artery.

lower forearm, and because its size is sufficient ordinarily to accept a 15 gauge needle or cannula.

Technic

The artery is exposed through a 1.5 cm. longitudinal incision over the radial artery immediately to the ulnar side of the styloid process of the radius. After incising the skin it is necessary to cut the fibers of the fascia before the

artery can be exposed. It is important to free the artery from its associated veins and other tissue. A section of the artery, at least 1 cm. in length, is isolated between two silk ligatures which are secured snugly by means of hemostats without actually tying or clamping the vessel. The artery may then be opened with a scalpel as indicated in figure 5a, by transfixing the artery transversely and withdrawing the scalpel distally and anteriorly thus making a three-cornered opening into which the cannula can be readily inserted (fig. 5b and c). A short, longitudinal incision is also satisfactory but care must be taken not to incise the posterior as well as the anterior wall of the artery. The cannula is inserted and secured in place by tying it with the proximal ligature. Pressure is applied to the fluid in the container. The clamp is removed from the rubber tubing and the blood is allowed to flow into the artery. At the beginning of the procedure the pressure exerted on the fluid may be between 200 and 300 mm. of mercury. The blood pressure is checked at intervals of one minute either by the conventional method on the other arm or by reducing the pressure over the fluid until the flow is arrested as visualized in the Murphy drip. At this point the two pressures, i. e., the pressure registered by the manometer and that in the radial artery, are almost equal provided the level of the fluid in the container is held at the same level as the heart of the patient. When the patient's pressure is found to have reached what is considered a safe level, as for example, 90 mm. of mercury, pressure over the fluid is reduced so that there is a slow, continued flow. Fluid may be given also by the intravenous route during this procedure. It is wise to keep the arterial cannula in place until there is reasonable assurance that the fluid loss has been made up and that the blood pressure has become stabilized. Then the cannula is removed and the artery is either ligated or resutured. Ligation of the artery seldom, if ever, leads to any difficulty because of the rich anastomosis between deep and superficial palmar arterial arches. Indeed, in many subjects it is possible to occlude the radial artery by digital pressure 4 or 5 cm. above the wrist and still to be able to detect a radial pulse in the wrist owing to the presence of this anastomosis. However, it is not a difficult matter to resuture the artery using No. 7-0 silk on a round, atraumatic needle as indicated in figure 6.

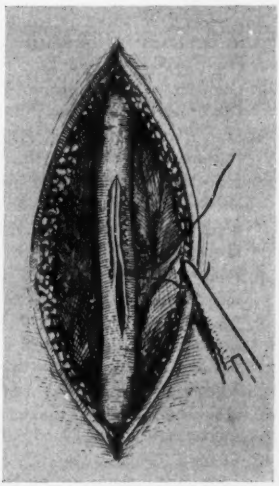


FIG. 6. Suture of artery after removal of cannula, using 7-0 silk on a round atraumatic needle.

If arterial infusion is to be used in the treatment of conditions which most clearly indicate it, namely, severe hemorrhagic hypotension, the equipment must be available on a moment's notice, and the persons who are to apply it must be familiar with the technical details.

Summary

Arterial infusion is a valuable procedure in the treatment of low or absent blood pressure as a result of extensive hemorrhage.

References

1. Langendorf, cited by Birillo, I. A. 7
2. Crile, G. W.: Anemia and Resuscitation (New York: D. Appleton and Company, 1914) p. 9.
3. Seeley, S. F., cited by Kohlstaedt, K. G. and Page, I. H.: Hemorrhagic hypotension and its treatment by intra-arterial and intravenous infusion of blood. Arch. Surg. **47**:178-191 (Aug.) 1943.
4. Gardner, W. J.: Control of bleeding during operation by induced hypotension. J.A.M.A. **132**:572-574 (Nov. 9) 1946.
5. Harris, H. E. and Hale, D. E.: Induced hypotension in control of bleeding during fenestration operation. Tr. Am. Acad. Ophth. 90-96 (Nov.-Dec.) 1947.
6. Hale, D. E.: Controlled hypotension by arterial bleeding during operation and anesthesia. Anesthesiology **9**:498-505 (Sept.) 1948.
7. Birillo, I. A.: Intra-arterial blood transfusion in shock, agony and cardiac arrest. Khirurgiya No. 8, 3-17, 1939.
8. Kay, E. B. and Hacker, V. D.: Treatment of shock by aortic transfusion during thoracic operations. J.A.M.A. **134**:604-605 (June 14) 1947.
9. Love, J. G., Courtin, R. F., Anderson, C. D., and Lundy, J. S.: Hypotension induced by arteriotomy, using Page's technic, an aid in surgery; its use in the removal of an epidermoid tumor of the third ventricle: report of case. Proc. Staff Meet. Mayo Clin. **23**:153-158 (March 31) 1948.
10. Robertson, R. L., Trincher, I. H., and Dennis, E. W.: Intra-arterial transfusion. Surg., Gynec. and Obst. **87**:695-704 (Dec.) 1948.
11. Glasser, O. and Page, I. H.: Intra-arterial transfusion in treatment of experimental hemorrhagic shock. Cleveland Clin. Quart. **14**:121-125 (April) 1947.

DIABETES

The following abstracts conclude the proceedings of the Diabetes course presented by the Frank E. Bunts Educational Institute on March 17, 1949. The first portion of these proceedings appeared in the July issue of the Cleveland Clinic Quarterly.

HYPERINSULINISM

R. W. Schneider, M.D.

Rational management of the many causes of hypoglycemia must be directed at the surgical removal of the cause, or the employment of medical measures designed to control the occurrence of low blood sugars. Surgery is indicated in only a small percentage. Among the larger medical group, dietary management highly successful in controlling one type, may at times intensify the hypoglycemia in others. Differential diagnosis at times may depend upon such a therapeutic test. Approximately 80 per cent of all cases are of functional origin. The hypoglycemia attending Addison's disease, Simmond's disease, severe renal glycosuria, lactation, Von Gierke's disease, severe inanition, or following gastric resection are usually quite easily recognized. Liver disease does not usually produce significant hypoglycemia until advanced hepatic insufficiency has occurred. By this time such patients are generally gravely ill and show other clinical signs of liver disease. Hypoglycemia associated with pituitary failure is less readily separated, but here there may be x-ray evidence of destruction of the clinoid processes, visual field changes, low urinary excretion of follicle-stimulating hormone and 17-ketosteroids, as well as clinical evidence of hypogonadism.

In hyperinsulinism due to islet cell adenoma, islet cell hyperplasia, or islet cell carcinoma, the patient usually has some type of spell or attack. Usually, each attack follows the same general pattern as characterized the preceding one. The intensity of the attack tends to vary from time to time, but usually increases in both frequency and severity with time. They appear characteristically during sleep or in the early morning hours prior to breakfast. They are commonly precipitated by fasting, delayed meals or by exercise. The symptoms are promptly relieved by food. The increased food consumption either to prevent the attack or to allay hunger commonly leads to weight gain. Obesity may actually become so extreme as to introduce an added operative risk and increase the technical problem of the surgeon. The symptoms attending the attacks may be of a wide variety, but are usually of a similar type in the same individual. The symptoms in general behave similarly to those attending insulin shock in diabetic patients. They may include nausea, sweating, pallor, syncope, restlessness, muscular spasm or convulsions, apprehension, confusion, disorientation, mania or coma. The same attempts at dietary manipulation so uniformly successful in the control of functional hypoglycemia do not ordinarily modify the clinical features in this type of case. Blood sugar determinations are invariably below 50 mg. per cent fasting even in the absence of symptoms.

In contrast the fasting blood sugar level in functional hypoglycemia is normal and is not abnormally depressed by prolonged fasting. Hypoglycemic symptoms are usually mild and characteristically appear two to four hours after eating. The patient is less likely to be aware of the relationship between symptoms and the relief obtained from eating. Chronic fatigue, headache, or loss of appetite may be the only indication of ill health. Measures designed to prevent the normal postprandial rise in blood sugar, such as a low carbohydrate high protein diet with feedings between meals, invariably abolish the symptoms and the hypoglycemia.

Even in the best of hands, surgical failures are apt to occur when the diagnosis is correct. In Whipple's own series, 8 patients required a second operation to eliminate

the functioning adenoma. There are a number of reasons for surgical failure to correct hyperinsulinism. First, the tumor may be overlooked the first time. If it is in the body or tail of the pancreas, its favorite site, it can usually be seen or palpated with ease. Such tumors have a definite feel, are usually about the size of a marble, and can be palpated with the fingers and thumb, but when the lesion is located in the head of the pancreas the duodenum must be mobilized in order to identify its location. On rare occasions islet cell tissue may have an aberrant location.

Occasionally the removal of a pancreatic adenoma fails to induce a cure. This may be for a number of reasons. There may be another adenoma, since 15 per cent occur in multiple locations. A small percentage of patients having adenomas also have diffuse hyperplasia of all other islet cell tissue. Partial or total pancreatectomy has been done in many of these, but generally the end result is quite disappointing. In the remaining failures carcinoma with distant metastasis may be present. Among 149 cases of islet cell tumors known to cause hypoglycemia, 15 were accompanied by distant metastases.

Three principal reasons for advocating surgical exploration when the symptom complex described by Whipple is presented are outstanding. Permanent damage to cortical cells from repeated attacks of hypoglycemia has been observed. A few patients have had to be committed. Extreme obesity may appear to complicate the problem further when surgery ultimately is undertaken. It is often difficult to determine whether the lesion is benign or malignant even after adequate histologic study. It is well to remember that records in proved cases show 1 in 10 to have distant metastases.

DIABETES IN CHILDREN

*Henry J. John, M.D.**

There are about 120,000 children in the United States under 20 years of age who have diabetes. In my series of 6000 cases of diabetes, there were 500 in children. Of these 6000 diabetic patients 4.5 per cent of the total were in the first and 4.2 per cent in the second decade. The sexes were equally represented, 51 per cent in boys and 49 per cent in girls. An hereditary factor in the diabetic children was found in 31.5 per cent. Infection as a predisposing factor was present in 122 cases, the diabetes following the infection in from a few days to two months. Over a period of twenty-seven years 61 children, or 16.7 per cent of the total, have died; 83.3 per cent are still living. Coma has been the greatest cause of mortality which has accounted for 24 deaths over a period of twenty-seven years. In the cases of coma which I have personally cared for, the mortality rate has been 3.7 per cent. Abuminuria has appeared in 31.3 per cent of the children. Deaths from intercapillary glomerulosclerosis occurred in 11 children, accounting for 18 per cent of the total mortality.

The progress of children with diabetes is invariably good for the first two or three years. After that time complicating factors frequently enter into the situation such as breaking the diet or infections. As years go by, therefore, the diabetic child requires more and more insulin. This is largely due to the increase in weight in the child which requires increase in the calorie intake and, of course, additional insulin. Also, failure to stick by the diet and infections are likely to cause a need for increased insulin. Even children who have been carefully controlled by diet and were remaining on such a diet showed a need for increased insulin as the years passed. After ten, fifteen, or more years signs of arteriosclerosis, retinal hemorrhage, and albuminuria began to appear in about one-third of the children who were by this time adults.

Camps for diabetic children are helpful and greatly needed. Most of the children show considerable improvement during a properly supervised camping period. Their morale is improved, and the most encouraging feature is the complete transformation

of the few introspective, depressed children who begin to realize that there is much fun in life.

*By invitation. 10515 Carnegie Avenue.

DIABETES AND PREGNANCY

*Max Miller, M.D.**

The problem of diabetes and pregnancy has become more important with the steady increase in the number of potential diabetic mothers. This increase is the result of improvement in overall treatment. Today, one out of every 300 to 500 pregnancies is complicated by diabetes. Pregnancy often brings out "latent" diabetes as indicated by the observation of one-fourth to one-half of this special group in whom diabetes was first discovered during the course of pregnancy. The mere presence of reducing substance in the urine in pregnancy cannot alone, however, be taken as indicative of diabetes, until lactosuria and renal glycosuria have been ruled out. The glucose tolerance test, especially the intravenous type, is essential for accurate diagnosis.

Certain normal physiologic changes of pregnancy, such as the elevation of metabolism rate, increased pituitary activity, lowering of serum base and the greater tendency to ketosis, all combine to alter the diabetic status and make treatment more difficult. Vomiting during pregnancy and the muscular effort of labor may complicate diabetic regulation. The role of the fetus in producing insulin has been overestimated if one can judge from actual insulin requirements during the course of pregnancy. In 70 cases reported by White, only 10 needed less insulin, 14 did not change, while in 46 (or 2/3) the amount of insulin used in the last trimester represented an increase.

With good care pregnancy in the diabetic mother does not present a hazard to life today. However, toxemia occurs in 20 to 40 per cent of this group, as compared to 5 to 10 per cent in non-diabetic mothers, and polyhydramnios develops in 10 per cent, a much higher proportion than in the non-diabetic group. The danger of pregnancy chiefly concerns the fetus. Before insulin, fetal mortality was greater than 50 per cent and in many clinics today in the insulin era, the mortality is still 25 to 30 per cent. Special care, however, has been a potent factor in reducing the figures to 10 to 15 per cent. Babies from diabetic pregnancies tend to be larger than normal. Major congenital malformations are found in 2 to 3 per cent and neonatal complications, such as anoxia and cyanosis, occur more frequently. Fetal hypoglycemia is found perhaps a little more often, but seldom can be held responsible for clinical symptoms and is easily avoided by giving intravenous glucose during delivery.

The management of diabetes and pregnancy is somewhat complicated and requires the closest cooperation and supervision of the internist, obstetrician and pediatrician to bring about a successful outcome. A high protein, low salt diet seems to minimize and mitigate the occurrence of toxemia. Carbohydrate intake should exceed usually 175 or 200 Gm., but calories should be adjusted carefully so as to avoid obesity. Because fluctuations in insulin requirements and lability of blood sugar frequently occur in these cases, regular insulin has been the insulin of choice with protamine dosage adjusted downwards to avoid nocturnal hypoglycemia. Pregnancy is usually terminated at thirty-six to thirty-eight weeks, the exact time depending on the size of the fetus and presence or absence of complications, such as toxemia and hydramnios. The obstetrician should decide whether medical induction or caesarean section should be used for delivery, although the latter is looked upon with growing favor because of lessened danger to the fetus. Anesthesia should be minimal and least calculated to upset mother and fetus. Spinal anesthesia has proven of value.

Intravenous glucose during delivery will insure a normal or high blood sugar in the

baby at birth, but blood sugars at four to eight hour intervals for the first twenty-four hours can be obtained as a further check. Glucose may be given to the baby if the blood sugar falls below 40 mg. per cent and at the same time is associated with clinical symptoms. The baby should be treated as premature in most cases, and incubator and oxygen therapy used as indicated.

The status of hormone therapy as advocated by White and her associates is still a controversial one. The cost of hormone therapy and the difficulty in obtaining adequate hormonal assays make routine use of hormones impractical for the majority of diabetic pregnancies. Many observers believe that the favorable results obtained by Dr. White can be ascribed to meticulous medical, obstetric and pediatric care, since similar results are now being obtained at other clinics which provide a similar type of treatment without the addition of hormones.

*By invitation. Asst. Professor of Medicine, Western Reserve University.

DIABETIC RETINITIS

Roscoe J. Kennedy, M.D.

The etiology of diabetic retinitis is not well defined. As to whether glycosuria is of any significance is of doubt. Hyperglycemia is probably not the entire picture as many patients do not develop retinal changes for many years. Lipoid metabolism may be a factor. Hypertension and arteriosclerosis may play a part. There is no one known toxic or metabolic substance which causes the retinal changes in diabetes; uncontrolled diabetes is the only known factor. Elwyn feels that the hemorrhages must be considered the result of the dilation of the terminal vessel units and the hyaline and lipoid deposits in the retina in diabetes is the result of subnutrition and suboxidation in consequence of the persistent dilatation of the terminal vessels. He feels that the persistent dilatation of the pre-arterioles, capillaries, and post-capillary vessels in the retina is the immediate cause of the retinal changes in diabetes. The exact cause of this dilatation of the terminal vascular elements in the retina is not clear although it may be related to a persistent hyperglycemia.

The findings in diabetic retinitis are usually bilateral. In a series of 47 cases we found 4 of the patients to have bilateral retinal changes and only 2 to have unilateral changes. The changes primarily involve the posterior pole of the eye, being most commonly located between the superior and inferior temporal vessels. The disk is usually normal, and edema is not considered to be a constant finding in diabetes.

A severe complication is proliferating retinitis, which may occur without extensive hemorrhage into the vitreous but often follows a pre-retinal hemorrhage. Fortunately, this is a relatively rare complication. However, in our small series of cases, we have seen retinitis proliferans in 8 patients. In these cases, there is a primary formation of new blood vessels with secondary production of connective tissue.

Another complication is a rupture of a pre-retinal hemorrhage into the vitreous, causing a sudden loss of sight. This can usually be recognized by the fact that the patient states that his vision has been lost suddenly, and upon examination one finds that the fundus reflex is black.

The treatment of diabetic retinitis is unsatisfactory. Local treatment is of no value. The use of the eyes should not be too restricted. The use of rutin, vitamin C, vitamin P, etc. has not proved of value in influencing the retinal hemorrhages. The primary and basic treatment is that of the diabetes itself. The maintenance of a normal blood sugar does not mean that the hemorrhages will disappear as often they remain for many months after adequate blood levels are established. Nevertheless, an effort should be

made to establish a normal blood level until a better method of treatment is determined. One must always be on the alert for any glaucomatous changes.

The prognosis is not too hopeful since sooner or later nearly all cases of diabetes develop retinal changes, although the prognosis as to life is good. These changes must be accepted as a component part of diabetes and not as a complication.

NEUROLOGIC PHASES OF DIABETES

Louis J. Karnosh, M.D.

All physical disorders, if they are to have a practical and sensible classification should be presented from the standpoint of etiology and treatment. This applies particularly to the somewhat baffling neurologic entities associated with diabetes. Heretofore, any pain or discomfort occurring in a patient with diabetes has invariably been labelled "diabetic neuritis." Practically every kind of peripheral pain or paresthesia experienced by a diabetic patient has been given such an appellation.

"Neuritis" is a misnomer if for no other reason than that it implies an inflammation of a nerve which in diabetes is exceedingly rare, for diabetes is not an infectious disease.

If it is kept in mind that diabetes imposes two primary changes upon nerve tissue, a classification of diabetic neurologic disorders will not be too much of an anatomic nightmare. Being essentially a deficiency disease, diabetes produces a degeneration of the myelin sheath, i.e. the insulating material of the nerve fiber suffers chemical disintegration. The demyelinization which first occurs is usually in the most distal nerve fibers but can be found anywhere along the course of a nerve trunk, and even in the region of the posterior roots. The same process, in severe and neglected cases, may ascend into the spinal cord, along the posterior column and up into the white matter of the brain. Hence, almost any kind of neurologic symptom, both peripheral and central can occur in diabetes as it does in all deficiency diseases, and it may be anything from a mere tingling or burning of the toes to a true organic dementia.

The second major type of neurologic defeat in diabetes is one which develops secondarily to vascular disease to which almost all diabetic patients, particularly in the older age ranges, are susceptible. Such neurologic disorders are considered to be due to ischemic changes in the nerve tissue. Again such changes may occur in the very distal portions of the nervous system or may develop in the cord and brain substance. In certain instances degenerations secondary to vascular disease can be observed directly with the ophthalmoscope in the fundi of the chronic diabetic patient.

Accordingly, any feasible classification of diabetic neurologic disorders should be based upon this recognition of the two modes of disease production, namely the direct action on the myelin sheath and the effect upon nerve tissue produced by ischemia.

Because the most distal nerves are primarily affected by myelin sheath degeneration and because the most peripheral vessels are usually the first to suffer arterial degeneration, diabetic nerve disorders have a striking predilection for the lower extremities and by far most of the aches, pains, and paresthesias of the diabetic patient are referred to the thighs, legs, and feet.

A. PRIMARY DIABETIC NEUROPATHIES

First to be considered are the disorders which can be assigned to primary degeneration of the myelin sheath. In this group it is assumed that the diabetic person is younger and that evidences of considerable arteriolar or peripheral vascular disease are not striking or are completely lacking.

I. Primary Diabetic Acroneuropathy. This disturbance is identical with the neuropathy of any deficiency disease such as pernicious anemia, beriberi and the early stages of so-called alcoholic polyneuritis. In diabetes it is almost entirely restricted to the feet,

which are the site of numbness, tingling paresthesias, burning sensations of the soles and of the dorsum of the feet. The disorder is always symmetrical and is likely to be most bothersome at night when the feet are under the covers. The patient finds some relief in rubbing the parts and expresses the idea that the circulation is poor.

Circulation, however, is adequate and objective vasomotor changes are not demonstrable. Neurologic findings are present but are usually overlooked. Early absence or diminution of the ankle jerks is the rule. Sensory defects do occur but are evasive. They consist of a blunting of the finer discriminative or gnostic sensations, such as appreciation of two points, of accurate localization and of position sense in the toes. Pain sensation, however, is actually exaggerated and the pin prick induces a rather diffuse and disagreeable experience over the sole even after the stimulush as been removed.

II. **Diabetic Radiculopathy.** This disturbance is the one which produces the most common and most severe forms of what the clinician calls "diabetic neuritis." The onset is relatively acute, and it may occur in the young person, in whom vascular disease is not suspected, as well as in the older diabetic patient. At the height of the process the degree of discomfort and disability is frequently severe. The pain is sharp, often excruciating, and is usually referred along the obturator, the femoral and less commonly the sciatic nerve. It is typical root pain. As in all neuralgic pains there is a paucity of objective sensory or reflex changes and frequently the patient is regarded as being neurotic. Proof that the condition is a true root disease is found in the fact that a large majority of these patients have an elevated protein in the spinal fluid and in every sense the condition simulates a tabetic root crisis.

III. **Diabetic Pseudo-tabes.** Diabetic patients in whom demyelinization of the sensory roots of the spinal cord causes neuritic pain, if neglected may develop an ascending degeneration of the posterior column of the spinal cord. This process is a familiar picture to the pathologist and the degeneration is almost identical with that seen in pernicious anemia. Such a patient develops ataxia, loss of tendon reflexes in the legs, loss of position sense, muscular hypotonia and flabbiness and even trophic ulcers. To complete the picture the pupils may become sluggish to light or even fixed, so that only a serologic test of blood and spinal fluid may be necessary to differentiate the condition from a true tabes dorsalis.

Treatment of these three neural degenerations is of prime importance because early and adequate care of diabetic acroneuropathy and of diabetic rediculopathy may prevent the third disorder, diabetic pseudo-tabes. The first two can be corrected but once the third process develops the outlook is decidedly poor.

If myelin sheath degeneration occurs in the peripheral nerves or even in the dorsal roots, the process can be reversed with usual diabetic control and with whatever supportive measures seem to be indicated.

Lewy (J. Nerv. and Ment. Dis. 89:1, 1939.) has emphasized the three vital measures in treating myelin sheath degeneration in polyneuropathy and root neuralgia. They are as follows: (A) Increase, not decrease the sugar intake, (B) Add enough insulin to utilize the additional carbohydrate, (C) Supplement every increase in carbohydrate with a parallel increase in Vitamin B. This means not only a liberal oral dose of all vitamin principles but daily intravenous administration of nicotinamide, 100 mg. and thiamine chloride, 40 to 50 mg. for a period of six to eight weeks. This program is particularly necessary in the management of a stubborn diabetic root pain, and the improvement can often be measured in this instance by the gradual reduction of spinal fluid protein to normal levels.

Analgesics for symptomatic relief of diabetic paresthesia or pain is an important item. Such drugs should always be used sparingly, for their use may mask the value of

the basic treatment. A favorite drug has been codeine which is often given in fairly high doses. Apart from its unfavorable side actions, it is prone to lead to habit formation and may be demanded long after genuine root pain has disappeared. Demoral is even worse and should be definitely avoided. The patient may justify its use on the claim that its withdrawal may cause a relapse of the neuralgic discomfort and at best it is difficult to deprive a patient of the general sense of well-being which the drug produces. Aspirin is safer because its action does not include a relief of psychoneurotic tension as do the true narcotics.

Since all neuropathies are regarded as disruptions of enzyme systems in the neurone, the use of a dithiol, particularly British Anti-Lewisite (BAL), should be considered in treating severe diabetic and other metabolic peripheral nerve diseases. (Furmanski, A. R.: Arch. Neurol. and Psychiat. 60:270, 1948). Inasmuch as the metabolism of carbohydrate in diabetes involves essential enzyme systems the use of BAL in diabetic neuropathy should be undertaken with caution.

It should be pointed out that even if the clinician succeeds in aborting the myelin degeneration in diabetes, there is a constant tendency to recurrence in a certain type of patient. Why this susceptibility should exist in one case and not in another is still an unanswered question. The degree of neuropathy is never parallel to the degree of diabetes. A patient with mild diabetes may develop a rapid and malignant degeneration of peripheral nerves and spinal cord while many older and pronounced diabetic patients may be utterly free of all neurologic symptoms.

The integrity of the liver, the hydrochloric acid of the gastric juice, phosphorus and sulphur metabolism and even the emotional state have all been implicated in this problem.

B. DIABETIC—VASCULAR DISORDERS

The second major group of neurologic disorders in diabetes are those due to vascular disease. Here, the nerve tissue suffers as a result of ischemia and the problem of the moment is the degeneration of the arterial wall and the development of obliterating arteriosclerosis which occurs not only in the peripheral tree but also in the blood vessels which nourish the spinal cord, the brain stem and the cerebrum.

I. **Ischemic Neuropathy.** This process produces pain by implicating the fine arterioles which nourish the nerve trunks themselves, namely the vasa nervosum. The whole subject of nerve trunk ischemia has been pursued with extensive investigations by Denny-Brown and Brenner. (Arch. Neurol. and Psychiat. 51:1, 1944), by Roberts (Am. Heart J., 35:369, 1948) and Porter and Wharton (J. Neurophysiol. 12:109, 1949). Early degeneration of the vasa nervosum causes ischemia of the nerve trunk which is invariably announced by deep pain. This occurs long before other tissues show objective evidence of vascular disease.

Ischemic neuropathy in diabetes has an insidious onset and is usually found in patients over 40 years of age. The incidence is twice as great in men as in women. Its symptoms are almost identical with those in the early stages of Buerger's Disease, and they consist of pain in the deep muscles of the thighs and legs, paresthesias of the feet and toes, and cramps, especially at night. Pressure over the calves and particularly along the course of the main nerve trunks elicits tenderness and exaggerated pain. The tendon reflexes gradually disappear. The trouble is always in the lower extremities with greater involvement being most distal where earliest evidences of obliterating vascular disease are detected.

The course is gradually progressive and discomfort increases in direct proportion to the advance of obliterating arterial disease. With the appearance of unmistakable circulatory defect, the pain becomes an intolerable ordeal which makes walking or

standing impossible. Occasionally considerable improvement after many months may occur if the vascular status of the limb improves.

Naturally, the only treatment of value is that which is directed toward improving peripheral circulation. Tobacco should be prohibited. Promoting vasodilatation by drugs, the use of mechanical devices such as the Hermann pump, rest in bed, the administration of analgesics and various surgical procedures utilized by the vascular surgeon are the measures indicated for treatment of ischemic neuropathy.

II. **Diabetic Ischemic Disease of the Central Nervous System.** Even though vascular disease may not exist in the brain of a diabetic patient, pathologic changes do occur in the cerebral tissues in the form of patchy degeneration or demyelinization. This is particularly true after several bouts of diabetic coma. Nonetheless such changes rarely produce mental or neurologic symptoms and in a relatively young diabetic person in the pre-arteriosclerotic years, the clinician rarely encounters symptoms or signs which can be rightfully called diabetic encephalopathy. Therefore, until vascular disease actually intervenes, it is doubtful whether diabetes causes any serious disturbance in cerebral function. Psychosis due to diabetes is usually a psychosis based on some irregularity in cerebral blood supply, and it is therefore natural to find that most disorders of the central nervous system in diabetes are assumed to be an expression of cerebral vascular disease.

By far the most frequent lesion of the brain in diabetes is cerebral thrombosis. This may occur in the self-same arteries which are susceptible to apoplexy in the aging individual with cerebral arteriosclerosis and without diabetes. There may be a preference for certain arteries in diabetic cerebral arteriosclerosis, but we cannot be sure. Perhaps the posterior-inferior cerebellar artery can be designated as the artery of diabetic thrombosis for fully 50 per cent of cases of thrombosis of this artery which produces the so-called syndrome of Wallenberg are found to be diabetics. Otherwise the arteriosclerosis of diabetes in every respect is the arteriosclerosis of old age with its predilection for the perforating arterioles arising from the middle cerebral artery and ending in the substance of the internal capsule.

Again, it must be pointed out that there is no direct parallel between the degree of diabetes and the degree of cerebrovascular disease. By and large the worst form of arteriosclerosis occurs in the mildest cases of diabetes and one is forced to the disturbing conclusion that the diabetes itself fails to provide a completely satisfactory explanation for the early incidence of cerebral vascular accident in the victim of that disease.

Frequently it is next to impossible to establish a metabolic balance in this type of patient because the sugar regulating mechanisms in the hypothalamus may be involved in the degenerative brain disease. Circulatory stimulants may be useful such as caffeine, coramine, and possibly nicotinamide. The anticoagulant principles, heparin and dicumarol, usually are not employed because of the difficulty in making a positive diagnosis of thrombosis as against hemorrhage.

There remain large gaps in the knowledge of why some diabetic patients develop degeneration of the myelin sheath, and why others suffer with premature arterial disease. The evidence seems to indicate that some etiologic factor or group of factors other than an elevated blood sugar or glycosuria are responsible but so far have kept their identity well concealed.

THE KIDNEY IN DIABETES

Robert D. Taylor, M.D.

The vascular lesion of diabetes which appears in the kidney was well named intercapillary glomerulosclerosis by Kimmelstiel and Wilson. They described a syndrome, which now bears their names, that accompanies this process. It consists of diabetes,

proteinuria, arterial hypertension, and dependent edema. The histopathologic abnormality is made up of widespread deposits of hyaline material between the capillaries of the glomerular tuft. Laboratory tests show depression of filtration rate which is greater in degree than the damage to tubular function. Proteinuria amounts to 2 to 5 Gm. per twenty-four hours and is accompanied by pyuria (1,000,000 to 10,000,000 white blood cells per twelve hours, Addis count) and cylindruria (100,000 to 500,000 per twelve hours) with little, if any, hematuria.

This process must be differentiated from chronic glomerulonephritis. Intercapillary glomerulosclerosis is always accompanied by diabetes which is usually long existent and often has been improperly treated. The degree of anemia in the renal disease of diabetes is usually less striking than in glomerulonephritis. Hematuria of more than 1.0 million cells per twelve hours is unusual while this is a diagnostic feature of glomerulonephritis. The rate of renal deterioration is customarily not as rapid among those patients with diabetes.

Management of this aspect of diabetes includes continued regulation of carbohydrate metabolism with diet and insulin. Because of the disproportionate damage between the glomeruli and tubules, glycosuria is not a reliable guide to insulin requirements. Hence, blood sugar levels must be estimated frequently. When edema is present, rigid restriction of dietary sodium to less than 1.0 Gm. per day is necessary. Ammonium chloride 1.0 Gm. four times daily is often helpful, and in some cases intramuscular injection of mercurial diuretics must be used. The last can be given as often as necessary with little fear of permanent renal damage.

If hypertension with headache is distressing, thiocyanate is helpful. This drug must be given with extreme care because the impaired renal function predisposes to toxic blood levels. It can be prescribed in the form of an elixir with equal volumes of elixir of phenobarbital. A teaspoonful of the mixture twice daily can usually be given for five to seven days without danger. After this period, the serum concentration of thiocyanate should be measured and the dosage adjusted so that the serum level does not exceed 8 mg. per 100 cc. The lowest effective concentration which controls headache should be maintained.

When azotemia appears, a diet that contains less than 0.5 Gm. of protein per kilogram of body weight per day will lessen the intensity of uremia and modify the unpleasant symptoms which accompany it.

DERMATOLOGIC PROBLEMS ENCOUNTERED IN DIABETES MELLITUS

E. W. Netherton, M.D.

From 20 to 25 per cent of patients with diabetes mellitus develop various dermatoses because of the disturbance of carbohydrate metabolism. With the possible exception of the xanthoma diabeticorum and necrobiosis lipoidica the dermatoses commonly observed in a diabetic patient are not pathognomonic of that disease.

Urbach and his associates determined the sugar content of 30 to 40 mg. of human skin and found that 68 mg. per cent was the upper limit of normal. They studied the glucose tolerance curve of the skin and found among other things that in the customary glucose tolerance test the glucose content of the skin reached its maximum level in one hour after ingestion of glucose, and dropped to normal more slowly than the blood glucose level. In diabetic patients, the skin glucose level did not reach its lowest level until four hours after eating. Furthermore, they found that in diabetic patients with skin manifestations the fasting skin sugar level averaged 82.8 mg. per cent and in diabetes without skin manifestations the fasting skin sugar level averaged 65.5 mg. per cent. In diabetes mellitus, the ratio between fasting skin sugar and blood sugar is increased.

The prolonged and increased storage of sugar in the skin of diabetic patients probably explains their susceptibility to pyogenic and mycotic infections.

Generalized pruritus with or without cutaneous manifestation is often an early indication of diabetes. Dermatitis of a nonspecific type may develop on any portion of the cutaneous surface; however, in severe diabetes a moist, weeping, intertriginous dermatitis may develop with predilection for the genito-crural region, beneath breasts and in other pendulous folds. Intermittent pruritus vulvae without visible changes in the vulva may be an early manifestation of diabetes mellitus and precede for days or weeks the appearance of a vulvitis. Likewise, recurrence of acute balanitis should suggest the possibility of potential or active diabetes.

The most common dermatoses seen in diabetic patients are those caused by pyogenic and mycotic infections. Those caused by pyogenic infections are recurrent furunculosis, carbuncles, erysipelas, ecthyma, folliculitis, suppurative paronychia, hidradenitis suppurativa and other pyodermas.

The common mycotic infections which frequently cause eruptions in diabetes mellitus are usually of two types (1) those caused by monilia albicans and (2) those produced by dermatophytons. The moist, vesicular, intertriginous dermatitis involving the genito-crural region and the folds of pendulous breasts and abdomens, are apt to be caused by monilia albicans. This fungus also may cause dry or moist paronychia, onychomycosis, perleche, and erosia interdigitalis blastomycetica, which is usually confined to the webs of the second and third interdigital webs of the fingers.

Dermatophytosis may be difficult to control in the diabetic patient. Chronic dermatophytosis of the feet is occasionally complicated by recurrent acute cellulitis of the leg. Such a complication is more serious in a diabetic patient. It is also thought by some observers that neglect of dermatophytosis of the feet, or injudicious use of strong keratolytic or irritative remedies in the treatment of this dermatosis contributes to the formation of gangrene of the toes. Gangrene of the toes and feet is a well known complication of diabetes and may be hastened or precipitated by secondary infection resulting from careless cutting of toe nails, paring of corns and warts on the toes and feet of the diabetic.

Pigmentation is a cutaneous manifestation sometimes seen in the diabetic. Xanthochromia, a yellow discoloration seen chiefly in the nasolabial folds and on the palms and soles, is at times observed. The causative pigment is carotin and a lipochrome. It is thought that because of its impaired function, the liver is inhibited in its conversion of carotin of the blood to vitamin A. Hemochromatosis, or bronze diabetes, is a rare disease in which there is cirrhosis of the liver, sclerosis of the spleen and pancreas and disseminated cutaneous hyperpigmentation similar to that seen in Addison's disease. Hemochromatosis has been observed in non-diabetic patients. The pigmentation is caused by deposit of hemosiderin, melanin and hemofuscin in the skin and various organs of the body.

Dermatoses related to the disturbance of lipoid metabolism in diabetes mellitus may be divided into three types, (1) Xanthoma diabeticorum, in which the cutaneous lesions usually develop quickly and are characterized by discrete, at times grouped, small bright red globular or acuminate papules with predilection for the buttock and extensor and flexoral surfaces of the arms. Lesions may occur elsewhere. When lesions are well developed, small yellow areas of discoloration appear at their apices. The xanthomata may simulate acute papulopustules. There is an associated hyperlipemia. Xanthoma diabeticorum disappears after institution of treatment for diabetes. (2) Xanthoma tuberosum, characterized by development of pink to yellow, smooth papules and nodules with predilection for elbows, knees, palms, soles, and at times tendons is occasionally seen associated with diabetes mellitus. There is a hyperlipemia and hypercholesterolemia. The xanthoma may or may not disappear following adequate control

of the diabetes. Some observers feel that when xanthoma tuberosum associated with diabetes mellitus disappears following control of the diabetes, it should be classified as xanthoma diabeticorum; however, the clinical characteristics of the cutaneous lesions differ from those of diabetes xanthoma previously mentioned. (3) In the majority of cases of necrobiosis lipoidica which have been reported, there has been an associated diabetes mellitus. However, it has been observed in non-diabetic patients. Urbach was of the opinion that the non-diabetic patient with necrobiosis lipoidica should be considered as a potential diabetic and observed and studied with this possibility in mind. The cutaneous lesions of necrobiosis lipoidica have a predilection for the anterior and lateral surfaces of the legs. They may, however, develop on the arms and trunk. They are usually bilateral. The initial lesion is a small, flat, bright red, smooth papule. The lesion enlarges by peripheral extension to form variable sized, rounded or irregular plaques. As the lesion enlarges, its margins remain red to at times violaceous. The central portion develops a yellowish hue, with distinct atrophy of the epidermis. Telangiectases develop on the surfaces of the larger lesions. Ulceration may occur, but is not a common manifestation. Histologic changes consist of a homogenous degeneration of the collagen tissue without subsequent necrosis. At the periphery of the areas of necrobiosis, there is a mild perivascular inflammatory infiltrate, consisting of histiocytes, lymphocytes and occasional leukocytes. The vessels show varying degrees of obliterative changes. Necrobiosis does not tend to disappear with control of the associated diabetes. In some cases spontaneous improvement has been observed.

Cutaneous manifestations caused by insulin such as generalized urticaria and focal reactions at the site of injection may occur, in a diabetic patient. Focal panniculitis followed by atrophy of the subcutaneous fat, the development of lipoma-like masses at the site of repeated injections of insulin, as well as the formation of abscesses and ulcers are infrequent complications of insulin therapy.

DIAGNOSIS AND TREATMENT OF CORONARY HEART DISEASE

A. Carlton Ernstene, M.D.

Arteriosclerosis is one of the most important complications of diabetes mellitus, and because of this and the age distribution of that disease, coronary heart disease is of common occurrence in the diabetic patient. The principal clinical manifestations of coronary heart disease are angina pectoris, acute myocardial infarction, acute coronary failure, paroxysmal cardiac dyspnea, certain disturbances of heart rhythm, and congestive heart failure.

Angina pectoris is a descriptive term applied to attacks of paroxysmal pain or discomfort in the chest which are induced by exertion or emotion and are relieved promptly by rest or termination of the emotional episode. The most important measure in the treatment of the condition consists of having the patient do all that is possible to avoid the attacks. Hurry, heavy lifting, excitement and exposure to cold must be avoided as completely as possible, and all patients should be instructed to rest in a chair for thirty or forty-five minutes after each meal. Every patient should receive a thorough trial on one of the purine derivatives, such as theobromine and sodium acetate, for in a certain number these preparations result in a distinct improvement in the individual's exercise tolerance. Mild sedatives should be administered to all patients who are unduly concerned about their condition or are of an excitable nature. Every individual should be supplied with a number of nitroglycerine tablets, gr. 1/200, with instructions to use one whenever an attack is not relieved by rest within one minute.

Acute myocardial infarction is characterized, in all but a few cases, by pain similar to that of angina pectoris but generally more severe and almost always of longer duration.

Symptoms of shock of mild to severe degree appear soon after the onset in practically all patients, and fever and leukocytosis usually develop within twenty-four hours. The electrocardiogram shows diagnostic changes in practically every case if records are made every day or so and if multiple precordial leads are used in addition to the standard limb leads.

The first aim in the treatment of acute myocardial infarction is to relieve the pain. Morphine remains the most valuable drug for this purpose although papaverine hydrochloride or aminophyllin by intravenous injection gives prompt relief in certain patients. Atropine sulfate, gr. 1/150, is administered by subcutaneous injection every eight hours during the first three or four days as a possible means of preventing the occurrence of ventricular fibrillation. Severe shock may be combated by the slow intravenous administration of plasma. Oxygen is administered for the relief of prolonged pain, cyanosis or intense dyspnea. Dicumarol is given for at least three weeks provided that facilities are available for measuring the prothrombin time of the blood and provided the patient does not have renal or hepatic insufficiency or a blood dyscrasia with hemorrhagic tendencies. Digitalis is administered only to patients in whom evidence of congestive heart failure develops or in the event of auricular fibrillation with a rapid ventricular rate. The patient is kept in bed for six to eight weeks, depending on the severity of the attack, and is not allowed to resume his business or professional activities until he has been up and about for approximately the same length of time.

Certain patients who have coronary artery disease, experience attacks of substernal pain of longer duration than the pain of angina pectoris but do not subsequently present clinical or electrocardiographic evidence of myocardial infarction. The term "acute coronary failure" has been applied to this syndrome. Treatment consists of the administration of morphine or the intravenous injection of papaverine hydrochloride or aminophyllin to relieve the pain. The patient is kept in bed for ten to fourteen days rest and during this time dicumarol is administered as in the management of acute myocardial infarction.

Coronary artery disease is a common cause of acute left ventricular failure which results in paroxysmal cardiac dyspnea or cardiac asthma. The most effective measures in the treatment of an attack are assumption of the upright position and the administration of morphine sulfate or the intravenous injection of aminophyllin. All patients who have experienced a seizure should be digitalized and placed on a low sodium diet. If there have been severe or repeated paroxysms, mercurial diuretics should be administered daily or every other day until the drug no longer causes diuresis or loss of weight.

Coronary heart disease may be responsible for any one of the recognized disturbances of cardiac rhythm. It is the most common cause of auriculoventricular block which may be of any degree from simple lengthening of auriculoventricular conduction time to complete dissociation of the auricles and ventricles. The higher grades of block may be complicated by the Adams-Stokes syndrome. Adams-Stokes seizures are rare, and the actual attacks usually are of such short duration that they do not require treatment. In rare instances, however, the ventricular standstill is of such duration that life is threatened and the intracardiac injection of epinephrine hydrochloride, 0.5 to 1.0 cc. of 1:1000 solution, is indicated. The most effective drugs for preventing recurrent attacks are epinephrine hydrochloride, 0.3 to 1.0 cc. of the 1:1000 solution, subcutaneously or intramuscularly every two to four hours, ephedrine sulfate by mouth in doses of $\frac{3}{8}$ to $\frac{1}{2}$ gr. every four to six hours, and paredrine by mouth in doses of $\frac{2}{3}$ to 1 gr. three or four times a day.

Coronary artery disease often results in the gradual or rapid development of symptoms and signs of congestive heart failure. Treatment does not differ from that of myo-

cardial failure due to other types of heart disease and consists principally of absolute rest in bed, the proper administration of digitalis, sedatives, and diuretic drugs, restriction of the sodium content of the diet, and, less often, venesection and the mechanical removal of fluid from the thorax.

INDICATIONS FOR SURGERY IN DIABETIC GANGRENE

George S. Phalen, M.D.

The introduction of the sulfonamide compounds and penicillin has greatly altered the clinical course of cases of diabetic gangrene. With these drugs to combat the associated infection, the diabetes may be brought under control by medical management prior to amputation. Ten or fifteen years ago, diabetic gangrene was considered a surgical emergency; usually a high amputation was performed to get well away from the gangrenous area and to be certain of adequate circulation and healing of the stump. If the spread of infection was not promptly checked by radical amputation, the diabetes could not be controlled, and death from overwhelming sepsis was inevitable. Nowadays, with the use of antibiotics, the surgeon may not even see the patient with impending diabetic gangrene, since with proper medical treatment these cases may never need an operation. Furthermore, less radical amputations may now be performed without endangering life.

The site and type of amputation depend upon a clinical evaluation of the part. A great deal can be predicted about the viability of a member by a simple examination. Is the foot warm to touch, or does it have a perfectly cold cadaverish feel? If good sensation is present in the skin, there is usually adequate circulation beneath it. The color and elasticity of the skin also gives the surgeon a good idea about the circulation.

Palpation of the arteries in the lower extremity is also of great importance in deciding about the site and type of amputation that may be done. If both anterior and posterior tibial arteries are palpable, a local amputation of the gangrenous toe may be performed. If only the posterior tibial artery is palpable, a local amputation may still be done in many cases. If there are no pulsations palpable about the foot, but the popliteal pulse may still be felt, an amputation below the knee may be considered. If pulsation in the femoral artery is either weak or absent, amputation at a level above the knee is necessary.

If there is edema over the dorsum and sole of the foot which does not subside after a day or two of bed rest and with control of associated infection in the foot, it is likely that local amputation will not suffice. If the area of gangrene is sharply localized to one or two digits, the surgeon may be able to do a local amputation—either a simple guillotine amputation of the toe itself or a resection of the entire toe together with its metatarsal, (the "pie operation," so-called because the section of tissue removed is wedge shaped like a piece of pie). If there is severe pain in the involved foot, the surgeon may be relatively certain that a local amputation will not effect a cure.

There are many factors that affect the site of amputation. It is of primary importance to select a site that is relatively certain to heal. It is a simple matter to ascertain the adequacy of the circulation at the level of the amputation when the surgery is being performed. Since a tourniquet is not employed at the time of the operation, the surgeon has only to observe the amount of bleeding present and the viability of the tissues at the level of the amputation. If the circulation is obviously inadequate at the first level, it is certainly better to proceed immediately to a more proximal level rather than subject the patient to more than one operation. In some cases, the extent of the gangrene may not be appreciated prior to the operation. For example, a single toe may appear gangrenous and the anterior tibial vessel may have a palpable pulse; but at the time of operation

it will be seen that the ischemic necrosis involves not only the toe but also the wedge of tissue, including the toe and its metatarsal, which is supplied by the dorsal metatarsal arteries distal to the arcurate branch of the anterior tibial artery. In such a case, simple amputation of the toe will not suffice and a "pie operation" must be done.

In choosing the site of amputation, some consideration must be given to the functional value of the stump. A useful foot may remain after amputation of one or all of the toes, after a "pie operation" involving one or two rays (a toe plus its metatarsal), or after an amputation through the base of the metatarsals. Amputation farther proximal in the foot does not give a satisfactorily functioning stump. In an amputation below the knee, an attempt should be made to leave about a six-inch stump. If there is any doubt about the circulation at this level, it is usually better to go ahead with an amputation above the knee. A supracondylar amputation usually suffices, but occasionally it is necessary to amputate through the middle or upper thigh.

The age and financial status of the patient may play some part in deciding about the site of the amputation. As a rule, amputations below the knee are not satisfactory in patients past sixty years old, since the stump is almost certain to ulcerate or become painful later and re-amputation at a higher level will be necessary. In some instances, the patient may not be able to afford a prolonged period of hospitalization in the hope of saving his limb at a lower level. This patient may insist upon having an amputation at a level which will be sure to heal and enable him to leave the hospital in the shortest possible time.

If a patient already has one leg amputated above the knee, every effort should be made to salvage a stump below the knee on the other leg; or if at all possible, a local amputation should be attempted.

In performing an amputation in cases of diabetic gangrene, the guillotine type of amputation should be done if the site of amputation is adjacent to the level of demarcation. A secondary closure then may be done a few days later if circulation appears adequate in the stump, or re-amputation at a higher level may be necessary. In cases of extensive gangrene involving the entire foot where it is still felt advisable to attempt to save the patient a stump below the knee, it is much the safer procedure to do a guillotine amputation at the most distal site where circulation appears adequate. Then a secondary amputation at the site of election, six inches below the knee, may be performed within a week or ten days if there is no evidence of progressive cellulitis or gangrene.

If the site of amputation is far removed from the site of the gangrene, as a supracondylar amputation in a case of gangrene involving only the foot, then an amputation may be performed with primary closure of the stump. A soft rubber drain is always left in these stumps, however, to prevent formation of a hematoma with subsequent infection. This drain is removed in twenty-four to forty-eight hours if there is no evidence of infection or hemorrhage in the stump.

Occasionally, as in the "pie operation," small catheters may be sewed in place and the wound loosely closed. This permits irrigation of the wound with antibiotics, such as penicillin or streptomycin, to control infection and promote healing.

PRE AND POSTOPERATIVE CARE OF THE DIABETIC PATIENT

E. Perry McCullagh, M.D.

Last year in 400 new patients with diabetes the diagnosis was first arrived at in 20 on the basis of hyperglycemia in a random blood sugar test and in the absence of glycosuria in the first urine test. This was 5 per cent of all cases. In these 20 patients the diagnosis would have been missed if the blood sugar had not been estimated.

It is a matter of considerable value to the patient for his physician to know of the presence of even mild diabetes before surgery and to make suitable plans to combat it because acidosis or coma may develop if sufficient stress is imposed. Its presence, though mild, may have an important bearing on the healing of tissues or if not recognized in time postoperative complications or infections already may have established considerable acidosis before the disease is acknowledged or treatment begun. For such reasons as these we believe that all patients should have a routine blood sugar test and that it should be reported and considered before surgery is started.

The management of diabetes in the surgical patient can be considered from several angles:

(1) Differential diagnosis of symptoms due to acute abdominal conditions or acidosis;

(2) Decision as to treatment and timing of necessary operations in acidosis;

(3) The handling of diabetes in cases of elective surgery;

(4) Preoperative preparation of patients with diseases having a special relationship to diabetes;

(5) A plan for handling of diabetes on the day of surgery;

(6) Postoperative treatment and feeding of surgical patients;

(7) The diagnosis of surgical complications during acidosis or coma.

When a patient is seen in severe diabetic acidosis the diagnosis usually is readily established by the clinical appearance, vomiting, the flushing, dehydration, dyspnea, glycosuria, ketonuria and the determination of hperglycemia and a carbon dioxide combining power below 35 volumes per cent.

In all such patients various procedures are carried out as treatment is begun. These include careful consideration of signs of shock or circulatory failure, a search for infection, treatment of gastric dilatation or fecal impaction.

Under these conditions the only decision which ordinarily concerns the surgeon as well as the internist is the problem of abdominal pain and whether or not the pain may mean appendicitis which has precipitated the acidosis.

The differentiation usually can be confirmed by several means. If a good history is available it will show that appendix pain preceded coma—acidosis pain followed the symptoms of acidosis.

Acidosis pain tends to be more general than appendix pain and may involve the back and limbs or at times simulate coronary thrombosis. If fever is present, which applies to both conditions and if leukocytosis is high (and it may be over 50,000 in acidosis) these findings are of no help.

If the carbon dioxide combining power is below 35 volumes per cent surgery should not be attempted unless it is imperative. A situation seldom exists in which the patient cannot wait safely for two hours. During this time the use of adequate amounts of intravenous Ringer's solution or saline will almost entirely have eradicated the pain of acidosis while that of appendicitis remains and by that time localized tenderness may be elicited clearly and rigidity become more local.

If the carbon dioxide is 35 or above and doubt still exists, surgery is preferable to the risk of further delay.

In elective surgery the problem is entirely different. Under these circumstances diabetes should be thought of, not in terms of normal blood sugar levels alone, but in the health of the body. If the diabetes is mild and the patient in a good state of general

health, two or three days in the hospital may be well spent in obtaining good diabetic control and in becoming acquainted with insulin requirements.

In older patients, and especially malnourished ones, who come for elective surgery such as an herniorrhaphy when surgery of the skin or surgery of the extremities is involved, it is preferable to postpone surgery for one or two months. During this time not only adequate control can be established and maintained but a correct diet will have repaired many of the changes of chronic malnutrition. Strenuous weight reduction should be postponed until a later date and in the preoperative period not only are adequate calories advisable but a relatively high protein intake as well.

The procedure followed in the average case is a simple one. The full diet is maintained until the day of operation. This is important particularly in hyperthyroidism and in liver disease. On the day of operation blood and sugar determinations are done fasting. If protamine insulin is being used the dose is cut to one-half of the total as in the neighborhood of 40 units or to about ⅓ if 60 units or more have been required daily. If the operation is to be performed in the morning hours, breakfast is omitted and no regular insulin given. If the operation is scheduled for afternoon a liquid breakfast is prescribed and a third of the usual daily allowance of insulin given as regular insulin. Immediately after the operation an intravenous injection of saline or Ringer's solution of 1000 or 2000 cc. is prescribed. This contains 5 per cent glucose and to the solution is added 25 to 50 units of regular insulin for each 100 Gm. of glucose allowing the maximum in severe diabetes and the minimum in mild cases.

The blood sugar level is followed 2 or 3 times daily when the disease is severe and once daily when mild. Urine is tested on the ward for sugar every four hours and regular insulin is given every four hours, the dose varying from 2, 3 and 5 units to 5, 10 and 15 in cases of varying severity based on yellow, orange or red Benedict's tests.

As soon as possible food is given by mouth. Except where gastrointestinal surgery prevents it, clear liquids can usually be given in small amounts the first postoperative day, frequently in such a way as to make up the usual available glucose content of the diet. At first tea with sugar may be most readily accepted, gingerale may be used, and often pieces of cooked fruits may be taken without gastrointestinal disturbances. Large amounts of raw fruit juices such as orange or grapefruit juice are more likely to cause disturbances.

When caloric needs are high as in cases of liver disease, it may be advisable to continue intravenous glucose daily in repeated doses supplying a total glucose intake as high as 300 or 400 Gm. per day.

In infants or patients with bladder or prostatic surgery where urine may not be obtained readily or at frequent intervals to guide the plan of insulin doses the blood tests may be depended upon more than they would be otherwise.

Ketosis is always prevented when possible but during the first few postoperative days blood sugar levels of 150 to 250 fasting or four hours after meals may be permitted. In patients who have undergone eye surgery where the disturbance of a reaction may cause damage to the eye and in those who have coronary sclerosis low levels of blood sugar are avoided carefully.

When the patient begins to eat if vomiting seems likely and the actual food intake is not easy to predict, the insulin dose can sometimes be given more accurately by withholding the insulin until thirty to forty-five minutes after each meal.

For patients requiring clear liquids as in bowel surgery the entire glucose content may be given as tea or coffee with sugar, or as pieces of cooked fruit and gelatine mix-

tures. In many instances strained orange juice or grapefruit juice may be used and in some condensed or raw milk with no harmful effects. By the second postoperative day most surgical patients may take a liquid diet the equivalent of and supplying their usual food intake.

PERIPHERAL VASCULAR DISEASE AND DIABETES MELLITUS

Fay Le Fevre, M.D.

The only peripheral vascular disease of importance associated with diabetes mellitus is arteriosclerosis obliterans. The occurrence of arteriosclerosis obliterans is eleven times more frequent in diabetic patients than in a comparable non-diabetic group.

Early recognition is important. All diabetic persons should have a careful vascular survey and evaluation. Clinical diagnosis of arteriosclerosis is readily made. History of leg fatigue and typical intermittent claudication is common. By observing gross temperature changes, color changes, and quality of peripheral pulsations the diagnosis can usually be established. X-ray evidence of arterial calcification does not always mean that the patient is having symptomatic peripheral vascular disease.

The first principle of treatment is well controlled diabetes. There is no single approach but a combined effort using all possible methods should be made. Treatment of diabetes without clinical evidence of arteriosclerosis obliterans should consist of general foot care, foot hygiene, and fungus prophylaxis. Regular observation and checking for early evidence of vascular disease is also necessary. The diet should be low cholesterol particularly if the blood cholesterol is elevated.

The diabetic patient with early signs or symptoms should be given general foot care and Buerger-Allen exercises and careful use of heat. Contrast baths are not desirable; physical therapy consisting of whirlpool baths and pavex are useful. There is still evidence that the latter form is helpful in simple intermittent claudication on the basis of arteriosclerosis obliterans. Caudal or sympathetic lumbar blocks to determine the degree of temperature rise with thought of considering sympathectomy may be employed. Medication is of little value. Nicotinic acid, thiamin chloride, thyroid, iodides, or Priscoline can be tried. In our experience, the following are of no value: tetraethylammonium chloride, histidine and vitamin C, tissue extracts, and anticoagulants.

The diabetic patient with rest pain and/or ulceration should have: (1) immediate hospitalization; (2) the use of the oscillating bed; (3) caudal blocks for relief of pain.

Local care of ulcers includes simple saline foot soaks, alternating with 1:5000 solution of potassium permanganate. The temperature of the soaks should be between 94 and 96 F. and last twenty minutes one or two times daily. Strong antiseptic solutions and excessive moist dressings should be avoided as tissue becomes macerated. Attempts to dry up ulcer areas, promote drainage and remove crusts carefully should be made. Also sympathectomy should be considered if the response from the caudal block is good. The value of anticoagulant preparations has not been established.

In all cases: (1) tobacco should be stopped; (2) protect from cold; (3) avoid trauma; (4) use heat with great caution.

A discussion of RENAL GLYCOSURIA by A. C. Corcoran, M.D., appeared in the October, 1948 issue of the Cleveland Clinic Quarterly.

PANEL DISCUSSION (Abbreviated)

(Drs. Miller, Browne, McCullagh, Le Fevre, Schneider, and Lazarow.)

Dr. Jordan: Here is the first question. If most diseases are treated at the onset, the chances of cure are greater. Then, why should not mild diabetes be treated with insulin?

Dr. McCullagh: It is a good idea to treat early diabetes with insulin. The possibility of relieving the individual of the necessity of taking insulin later should be sufficient reason for giving insulin at the beginning and trying it at least. Children who have diabetes ordinarily have rather abrupt onsets and it is relatively severe as soon as it is found. Insulin requirements under such circumstances vary tremendously. In some of the children I have seen I have been impressed by the fact that the insulin dose, a requirement that is perhaps in the neighborhood of 50, 70, 80 units per day the first week or two or perhaps even a few days, may fall to a point where one is tempted to withdraw it completely. Ordinarily the last 5 units or 10 units cannot be withdrawn and in the same individuals it has been my experience that after another few weeks or months, the dose requirement is relatively high again.

Dr. Jordan: Another question, "Is there a reliable micro-method for determining blood sugar levels in the office?"

Dr. Lazarow: There is a micro-method that we use on our rats all the time that requires only about 1/50 of a cc. of blood. However, the reducing method used in that determination is a ferricyanide and the precipitating agent is not quite specific so that non-glucose reducing substances are also measured. Consequently, the standards used will have to be higher taking into effect the glutathione and other things which are also measured. However, a method could be adapted from the other standard methods by using some of the microtechnics which are now being developed which probably could be done readily in the doctor's office.

Dr. Jordan: Here is a question addressed to Dr. Browne. "What is the general adaptation syndrome?"

Dr. Browne: The general adaptation syndrome is a term coined by Dr. Hans Selye which describes the set of body reactions, signs, symptoms, physiologic changes, and chemical changes which occur in the body in response to damage, stress, or illness. There are a whole host of responses which occur independently of the nature of the damage or the stimulus.

Dr. Jordan: "What is the nature of the change in the glucose tolerance test caused by malnutrition?"

Dr. Lazarow: It is known that many persons placed on a starvation diet may show changes in glucose tolerance similar to what is observed in diabetes. Placing them on a high caloric diet, particularly high fat, can improve the glucose tolerance.

Dr. McCullagh: From a clinical point of view, the most starved individuals we see, the thinnest, are those with anorexia nervosa. In them two distinct types of glucose tolerance occur. In persons who have anorexia nervosa for a long time there is good evidence that they develop not only insulin failure as a result of starvation but adrenal and pituitary failure as well. This seems to me a good explanation for the flat glucose tolerance curve which one may see in cases with severe anorexia nervosa.

Dr. Schneider: Perhaps protein, as Dr. Browne has shown, is handled differently under certain circumstances and I should think it might be quite true that carbohydrate would act in the same manner.

Dr. Jordan: Does an elevated blood cholesterol have any effect on vascular changes in the diabetic?

Dr. LeFevre: I don't believe we have a specific answer to that question. The evidence in animals indicates that, particularly in rabbits, one can produce vascular

changes with a high cholesterol diet which will tend to disappear on a low cholesterol diet. We do not have such evidence for humans. What meager evidence there is, tends to point to the fact that when the blood cholesterol is elevated, say over 200 mg. per cent, keeping the cholesterol down in the diet might help to retard arteriosclerosis. There has been no good clinical work done to prove that point, but I think we might assume there is some connection, the nature of which we do not understand, between cholesterol and the production of vascular changes or the premature production of vascular changes.

Dr. Jordan: Is it generally conceded that a low fat, high carbohydrate diet produces a definite drop in the blood cholesterol?

Dr. LeFevre: In reviewing my own cases on what we call a low cholesterol diet, we haven't definitely brought down the blood cholesterol.

Dr. McCullagh: A patient we hoped to show yesterday has xanthoma tuberosum of the type often seen in diabetes. However this type of xanthoma isn't necessarily associated with diabetes. A month ago this patient had a blood cholesterol value of 428. He was put on a low fat diet and two days ago his blood cholesterol was 224. This may or may not be significant, but seems unlikely to be explained on random sampling.

Dr. Lazarow: Has there been some change in his xanthoma?

Dr. McCullagh: Very little as yet.

Dr. Miller: I would just like to put in a plea for the poor patient who is at the present time being put on various diets for the value of which we do not have good experimental evidence. The diabetic patient has enough of a problem with the restrictions that already have been imposed without adding other changes of diet which have not been proved experimentally or conclusively in the laboratory or in the clinic. The relationship of blood cholesterols and the levels of cholesterol in diet certainly is not a close one. There is no close correlation. The ingestion of 10 Gm. of cholesterol over periods of months produces little change in the blood level and for that reason until further conclusive evidence is brought forth, I would be against introducing other radical changes in the diet in these patients.

Dr. LeFevre: I should like to ask Dr. Miller how he would bring about this conclusive evidence unless these patients are put on some form of diet.

Dr. Miller: I would agree with that if this is set up on an experimental basis with adequate control and careful observation. I do not think that indiscriminate application of diet of this sort, given at random by the doctor in his office, will ever bring forth conclusive evidence. Those are strong words, but it is my opinion.

Dr. Jordan: May I ask then how many members of the panel would put their patients on a low cholesterol diet under these circumstances and how many would not?

Dr. Lazarow: Well, I have no problem because my patients are all rats. I might point out that in the laboratory it has been impossible to produce arteriosclerotic changes no matter how much cholesterol you give a rat. In a rabbit you can. The question is are we closer to a rabbit than a rat?

Dr. Jordan: We had better move on to the next question. "Should protamine-zinc insulin be used in the presence of infection?"

Dr. Schneider: That is a matter of individual preference. I think that protamine-zinc insulin can be used in the presence of infection but certainly it is not the only insulin to be used in the presence of infection. If one has previous knowledge in a given case that, let us say, the insulin requirement is 60 units of protamine per day and the individual now has an acute infection, I see no reason why that person should not continue to receive that amount of protamine insulin. We expect, of course, that he is going to require a good deal more and why not then continue the 60 units of protamine insulin

and supply additional increments of regular insulin as frequently as is indicated by the clinical requirements? That would not be advocating the use of protamine-zinc insulin alone in the management of infection.

Dr. Jordan: Is it not possible to give protamine-zinc insulin in more cases at night rather than in the morning, not overlooking its accumulative effect?

Dr. McCullagh: Yes, it is quite possible that it can be used to an advantage by giving it at night in some patients. I think it depends on what is found to suit the particular patient best, what time the insulin is given as well as what type is given. When protamine-zinc insulin was first used in Denmark, it was given at suppertime or at bedtime, but Danish dietary habits differ somewhat from ours and most of us here take a relatively small breakfast, a somewhat larger lunch, and a good deal larger meal in the evening. In general this fits in well with the gradually increasing activity of protamine-zinc insulin when it is given before breakfast.

Dr. Miller: I assume, Dr. McCullagh, you are speaking of protamine-zinc insulin alone.

Dr. McCullagh: Yes.

Dr. Miller: Mark of New York and Ricketts of Chicago have written papers in which they have demonstrated that the accumulated use of protamine given over a period of days results in a constant action on the blood sugar. Under controlled conditions, same blood sugar curves were obtained regardless of whether protamine-zinc insulin was given at breakfast, at lunch, at supper, or at night. Consequently they drew the conclusion that it was immaterial as to when the protamine-zinc insulin was given under those particular conditions. It was usually given in the morning because it was more convenient. Of course, with the use of mixtures the rate of action of the insulin is much reduced and it is quite possible under those circumstances it might be better in certain cases to give it at other times.

Dr. Jordan: Another question on protamine-zinc insulin. Why do some patients not feel well on protamine-zinc insulin?

Dr. McCullagh: Apart from local reactions or allergic reactions which some people get (it is usually quite evident when it occurs) or from hypoglycemia, I know of no reason why protamine-zinc insulin produces any particular ill feeling.

Dr. Miller: I think that the use of protamine-zinc insulin alone in the older mildly diabetic patient may occasionally give rise to untoward symptoms. This is because the disease is essentially mild with normal fasting blood sugars which rise only after meals. Protamine insulin serves merely to intensify the process lowering the blood sugar before breakfast. It is quite possible these older patients may have insulin reactions, hypoglycemic reactions, which are not manifested in the ordinary way. Of course, too, in the presence of arteriosclerosis and coronary artery disease symptoms of a reaction may be different. We have had several cases in which the use of protamine-zinc insulin not justified on the basis of blood sugar levels has resulted in rather severe clinical symptoms which have been alleviated by the actual omission of insulin. We have seldom used protamine-zinc insulin in the older patient whose fasting blood sugar is normal.

Dr. McCullagh: You still think that, if these symptoms occur they are due to hypoglycemia?

Dr. Miller: Yes.

Dr. McCullagh: I agree.

Dr. Miller: What I am trying to say is that hypoglycemia in the older, mildly diabetic patient may not have the same obvious manifestations obtained with regular insulin. Therefore, the hypoglycemia should be watched for carefully.

Dr. McCullagh: It may produce only chronic fatigue.

Dr. Jordan: What is the pathologic-physiologic mechanism back of potassium depletion?

Dr. Browne: First of all, potassium tends to be lost from the intracellular water if cells break down. Therefore, under catabolic phenomena there will be a tendency for a loss of potassium from the body. After that has gone on for a certain period of time let us suppose that one is given glucose. This also happens, according to Dr. Thorn, in cases of Addison's disease treated with DCA. When one gives glucose, the potassium phosphorus for that matter tends to be deposited with the glycogen in the liver and elsewhere. An actual hypopotassemia may occur with a variety of signs and symptoms. At least part of the mechanism of potassium depletion is due first of all to its loss in the body associated with metabolism and secondly to the tendency to remove it by the use of glucose and insulin. There is a quite famous report on a diabetic child who, on recovering from coma, received 70 Gm. of sodium chloride per day. His blood pressure rose to about 170/110 and his diabetes disappeared. This happened spontaneously. When he ceased to eat, his blood pressure fell to normal and his diabetes reappeared. He then began to eat. He was taking in potassium. Subsequent raising of the sodium no longer led to this condition. It was only in the presence of a potassium poor or absent diet that this dramatic effect on carbohydrate tolerance occurred. I should like to know if anyone here has discovered what the mechanism of this is because it has always interested me. I feel that somewhere there is an explanation for a lot of things but I don't know what it is.

Dr. Jordan: We'll pass your question and any supplementary parts on to Dr. Lazarow.

Dr. Lazarow: I think I got into this because I want to amplify a little on what Dr. Browne said in relation to the glycogen story. It's been pretty fairly shown that for every gram of glycogen stored in the liver, it is stored with about 3 Gm. of water. Since water in the cell must be stored with electrolyte and since intracellular electrolytes are different from those which are present in the serum, namely high in potassium, when intercellular water is stored, intercellular potassium is stored as well.

Dr. Jordan: Do you have an explanation, Dr. Miller?

Dr. Miller: I was just as curious about that as Dr. Browne.

Dr. Jordan: Are there any acceptable books for the diabetic patient which may be used by him to supplement his medical supervision? Are there movie films available which may be instructive to groups of diabetics?

Dr. Schneider: One book which we have employed for a number of years is Joslin's "Manual for Diabetics." Dr. Henry John has a practical manual. There are other good ones.

Dr. McCullagh: Dr. Wilder has produced a good manual for diabetics; Dr. Bortz of Philadelphia produced one. There is a little book for patients called "The ABC's for Diabetics" with a great many pictures in it.

Dr. Miller: A book which we recommend is "Diabetic Care in Pictures" by Rosenthal. It has the advantages of having a profusion of pictures clearly done and also the text is not too complicated.

Dr. Jordan: Once three before meal blood sugars have been determined to be satisfactory on a given dose of insulin, will the relative blood levels remain the same on the same dose? How often should three a.c. blood sugars be done on an ambulatory patient to insure proper adequate control of the diabetes?

Dr. McCullagh: The answer to the first question is, "no," it will not necessarily stay put indefinitely. In fact, they don't stay put well at all. In some patients blood

sugars are always erratic and one of the policies perhaps in depending so much on blood sugars done before meals, or any other time for that matter, is that we know that they don't give us a picture which can be accepted as being constant.

The number of times, the frequency with which these tests should be redone is a matter of the judgment of the physician—it has to do with the severity of the diabetes. In general we like to have our patients come back to have the tests done a week or so after their first control and perhaps thereafter in three weeks or a month. The time they come back may vary between perhaps two and three months, as an average, and in less severe cases in four to six months.

Dr. Jordan: What is the relation of insulin to methionine metabolism?

Dr. Lazarow: In order to synthesize insulin it is necessary to have the constituents of amino acid which go into making the insulin molecule. The body is able to synthesize only about half the amino acids that are generally required and consequently an adequate supply of essential amino acids which the body cannot synthesize would be necessary. Since one of the constituents of insulin is cystine, which is a sulfur-containing compound and since probably the largest supply of sulfur-containing compounds enters the body as the amino acid, methionine, one would expect that at least requisite amounts of methionine or cystine would be necessary in order to insure insulin synthesis. The second aspect of the problem is the possible end relationship of methionine and glutathione. In the case of an alloxan diabetic animal, and it appears to be true following the injection of adrenocorticotropic hormone, there seems to be some relation between glutathione and diabetes. We have suggested that it may be an important prophylactic factor, but whether it is also true in human diabetes remains to be determined. However, if a glutathione factor should be important then methionine would also be involved since glutathione too contains cystine since it is probable that the major source of the sulfur of cystine comes from methionine.

Dr. Jordan: Can a patient get symptoms of hypoglycemia or resembling hypoglycemia with a relatively high blood sugar?

Dr. Miller: That is a difficult question. I think most of us have had the feeling that there are cases in which insulin reactions may occur at relatively high blood sugar levels. The converse is true also and we have much more evidence of that. The patients may be walking around with blood sugars as low as 30 and 40, particularly on protamine-zinc insulin without any obvious symptoms or signs of insulin reaction.

Dr. Jordan: Any other comment?

Dr. McCullagh: No, I agree with what Dr. Miller said.

Dr. Jordan: What are the EKG signs of hypopotassemia?

Dr. LeFevre: There are two major changes involving chiefly the S-T segment and the T wave. The usual changes are depression of the S-T segment and decrease in elevation of the T wave or flattening of the T wave.

Dr. McCullagh: Is there a prolongation of the Q-T segment?

Dr. LeFevre: It may or not be present. I don't think that it is as important as the depression of the S-T and T wave, although there may be some prolongation.

Dr. Jordan: How do you determine the initial dose of insulin?

Dr. Schneider: By trial and error. I think that the only point that is important is to emphasize again one thing about the administration of insulin. That is to remember always that insulin sensitivity may exist and it is always well to give the first dose perhaps a little smaller than you would be inclined to by the height of the blood sugar. The other factors that would determine the size of the dose of insulin, of course, would be the presence of complications, acidosis, infection, and so forth.

Dr. Jordan: Dr. McCullagh, how do you control insulin resistance?

Dr. McCullagh: You don't.

Dr. Jordan: What do you do when you have resistance? I think that is what the questioner means.

Dr. McCullagh: We just keep giving more and more insulin until we finally reach the point where the blood sugar is reasonably controlled. Sometimes that may take doses into the thousands of units per day. I have had one patient who required 1400 units per day. Such resistance may largely disappear which is a matter of mystery too.

Dr. Jordan: In other words, just keep going up until you get enough. That gets a little bit expensive sometimes.

Dr. McCullagh: It does, indeed.

Dr. Jordan: What is the proper procedure in mixing insulin for administration of insulin mixtures?

Dr. Miller: There are two methods—possibly three methods—which are being used. One is layering the insulin in a syringe, taking protamine zinc insulin first and adding the regular next. It is important, of course, to remember that you can't take insulin out of a sealed bottle without producing a vacuum. The air must be put in first. A good procedure is to put air in the regular insulin bottle and remove the needle. Then protamine zinc insulin may be obtained in the ordinary way, putting air in first and removing insulin. Then one can return to the regular insulin bottle and remove the insulin since the air has been previously introduced. This method sounds complicated but it is not nearly so complicated once it is tried. Another method which is unfortunately not available for most patients is that of having a premixed insulin. In this way you can get any insulin mixture desired: 2:1 mixture or 1:1 mixture and so forth. A few years ago Lilly Company supplied an oversized bottle which made it relatively easy to obtain any mixture required. At our hospitals—University Hospitals—we have a pharmacist prepare them. The average pharmacist often will not do it. There is no reason why the individual physicians could not mix insulin for their patients; a 2:1 mixture is the one most commonly employed at the present time.

Dr. Jordan: What are the indications and advantages of the 500 unit insulin?

Dr. Schneider: We still have too little experience in the use of 500 unit insulin, but the advantage would appear to be that those people with insulin resistance who require large doses of insulin can inject a smaller volume of solution.

Dr. McCullagh: It has a longer effect than if it were given in a weaker solution.

Dr. Jordan: Mason states, "In the case of the juvenile diabetic the blood cholesterol is a much better index of the completeness of the control than the blood sugar level." Is this the general belief today?

Dr. McCullagh: I think there is a great deal to be said on this point of view though I wouldn't go quite so far as to state it in those terms myself. I feel that the cholesterol is a valuable index of the control in the diabetic particularly when the blood sugars are erratic. We like to take blood cholesterols frequently in adults too, feeling that if the patient is out of control most of the time and just follows his diet two days before he is coming to see us, we may find that out from a high blood cholesterol when the blood sugar is normal.

Dr. Schneider: I agree with Dr. McCullagh. I think that perhaps a better criterion for determining satisfactory control of diabetes in children is their rate of growth, their weight, and their general sense of well being—their total nutrition in other words, regardless of what the cholesterol is.

Dr. Jordan: You think that is better than either laboratory test?

Dr. Schneider: I do.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

A continuation course will be presented on
Thursday, Friday, and Saturday November 17, 18, and 19, 1949

MEDICAL AND SURGICAL DISORDERS OF THE URINARY TRACT

Tentative Program

Thursday, November 17, 1949

8:00- 9:00 a.m.	Registration	
9:00- 9:45 a.m.	Motion picture—Kidney in Health	A. C. CORCORAN, M.D.
9:45-10:10 a.m.	Pyelonephritis and Glomerulonephritis	ROBERT D. TAYLOR, M.D.
10:10-10:30 a.m.	Technic and Significance of Addis Count and Urea Clearance	HARRIET P. DUSTAN, M.D.
10:30-10:50 a.m.	Renal Disease of Hypervitaminosis D	LEONARD L. LOVSHIN, M.D.
10:50-11:00 a.m.	Intermission	
11:00-11:20 a.m.	Renal Disease in Myelomatosis, Periarteritis, and Lupus Erythematosus	DONALD W. BORTZ, M.D.
11:20-11:50 a.m.	Management of Urinary Tract Infections Including Tuberculosis	EUGENE F. POUTASSE, M.D.
12:00- 1:00 p.m.	Luncheon—Courtesy of the Clinic	
1:00- 1:20 p.m.	Crush Syndrome	A. C. CORCORAN, M.D.
1:20- 1:40 p.m.	Unilateral Renal Disease and Hypertension	ROBERT D. TAYLOR, M.D.
1:40- 2:00 p.m.	Cystic Diseases of the Kidney	WILLIAM J. ENGEL, M.D.
2:00- 2:20 p.m.	Intercapillary Glomerulosclerosis	MAX MILLER, M.D.*
2:20- 2:40 p.m.	Congenital Anomalies of the Urinary Tract	J. G. WARDEN, M.D.
2:40- 3:00 p.m.	Renal Lesions in Childhood	WILLIAM J. ENGEL, M.D.
3:00- 3:20 p.m.	Intermission	
3:20- 3:40 p.m.	Nephrotic Syndrome	A. C. CORCORAN, M.D.
3:40- 4:00 p.m.	Kidney Tumors—Clinical Aspects	CHARLES C. HIGGINS, M.D.
4:00- 4:30 p.m.	Kidney Tumors—Pathologic Aspects	JOHN B. HAZARD, M.D.

GUEST SPEAKER

8:15 p.m. Clinical Significance of Hematuria . HERMAN L. KRETSCHMER, M.D.
Department of Urology, Presbyterian Hospital, Chicago

*By Invitation.

Friday, November 18, 1949

9:00- 9:45 a.m.	Motion picture—Kidney in Disease	A. C. CORCORAN, M.D.
9:45-10:10 a.m.	Electrolyte and Chemical Features of Uremia	A. C. CORCORAN, M.D.
10:10-10:30 a.m.	Nephrosclerosis and Hypertensive Renal Disease	IRVINE H. PAGE, M.D.
10:30-10:50 a.m.	Intermission	
10:50-11:10 a.m.	Dermatological Problems Encountered in Management of Urinary Tract Disorders	EARL W. NETHERTON, M.D.
11:10-11:30 a.m.	Cardiac and Electrocardiographic Aspects of Renal Failure	WILLIAM L. PROUDFIT M.D.

11:30-11:50 a.m.	Dietary Management of Uremia	G. M. C. Masson, Ph.D.
12:00- 1:00 p.m.	Luncheon—Courtesy of the Clinic	
1:00- 1.20 p.m.	Cystitis and Interstitial Cystitis	J. G. Warden, M.D.
1:20- 1:40 p.m.	Hyperparathyroidism	Robert W. Schneider, M.D.
1:40- 2:00 p.m.	Diagnosis and Treatment of Urinary Calculi	Charles C. Higgins, M.D.
2:00- 2:20 p.m.	Azotemia Precipitated by Sodium Depletion	Robert D. Taylor, M.D.
2:20- 2:40 p.m.	Production of Gastrointestinal Symptoms by Genitourinary Disorders	Eugene F. Poutasse, M.D.
2:40- 2:50 p.m.	Lower Nephron Nephrosis with Osteomalacia	Robert W. Schneider, M.D.
2:50- 3:00 p.m.	Intermission	
3:00- 3:30 p.m.	Prostatism and Prostatic Carcinoma	Charles C. Higgins, M.D.
3:30- 4:00 p.m.	Bladder Neck Obstruction in Women and Children	William J. Engel M.D.
4:00- 4:30 p.m.	Management of Acute Anuria	A. C. Corcoran M.D.
5:00 p.m.	Cocktail Hour—Wade Park Manor	

Saturday, November 19, 1949

GUEST SPEAKER

9:00-10:00 a.m.	Uremia	Louis Leiter, M.D. Clinical Professor of Medicine, Montefiore Hospital, New York
10:00-11:30 a.m.	Panel Discussion	

Questions pertaining to the urinary tract may be submitted in writing for the panel discussion. A "Question Box" during the first two days of the course will be available for the convenience of those wishing to present questions to the members of the panel.

REGISTRATION BLANK

The Frank E. Bunts Educational Institute . . . . . , 1949
Cleveland Clinic Building
2020 East Ninety-third Street
Cleveland 6, Ohio

Please register me for the course on "Medical and Surgical Disorders of the Urinary Tract" which is to be given November 17, 18, and 19, 1949. (Registration Fee is $15.00.)

I am enclosing check for $5.00 and the remainder will be paid on Registration, Nov. 17.

NOTE: Checks should be made payable to the Frank E. Bunts Institute. Mail registration blank and check to Dr. Edwin P. Jordan, Cleveland Clinic Building, 2020 East Ninety-third Street, Cleveland 6, Ohio.

Name . . . . . .

Address . . . . . .

Medical School and
date of graduation . . . . . .

This course is open only to graduates of approved medical schools. Registration will be limited to the number of physicians who can be adequately accommodated.

ANNOUNCEMENTS

Bunts Lectures

The Frank E. Bunts Educational Institute has scheduled the following Bunts lectures for 1950. These lectures will be held at the Cleveland Clinic at 8:15 p.m. Visitors are cordially invited.

January 23, 1950—Dr. A. C. Ivy
Recent Advances in Basic Knowledge of Gastrointestinal Tract

May 22, 1950 —Dr. Thomas E. Jones
Principles of Cancer Surgery

Meetings

Staff meetings are held at the Cleveland Clinic twice a month at 8:15 p.m. on Mondays except during the summer. All physicians are welcome to attend. The dates and subjects may be obtained in advance on request. A medical conference is held every Wednesday morning from 8 to 9 a.m. on the eighth floor of the Cleveland Clinic Foundation Hospital. A surgical conference is presented on Thursdays from 1 to 2 p.m. in the same place, and x-ray and chest conferences are given alternately on Tuesdays at 5:20 p.m. in the Founders and Staff Room of the Cleveland Clinic building. All of these conferences are also open to physicians who wish to visit them.

Appointment

Dr. Robert A. Hays has been appointed a member of the staff in the Department of Therapeutic Radiology. Dr. Hays graduated from Boston College in 1936 and from Tufts College Medical School in 1940. Following the completion of his internship at Worcester City Hospital, Worcester, Massachusetts, in 1942, Dr. Hays spent three years in the U. S. Army. He was granted a fellowship in the Cleveland Clinic in 1945 and was appointed to the assistant staff in 1949. Dr. Hays was certified by the American Board of Radiology in 1949.

INDEX

to

CLEVELAND CLINIC QUARTERLY

Volume 16 — 1949

A

Acute toxic ulcerative colitis; medical treatment of, 126

Adenoma; bronchial, 12

Amoebic hepatic abscess with bronchohepatic fistula, 142

Announcements, 59, 107, 183, 248

Arterial infusion, 216

B

Battle, J. D., Jr.: Thrombopenic purpura, 81

Bortz, D. W. and Haden, R. L.: Diagnosis and treatment of macrocytosis, 8

– The value of vitamin B_{12} in pernicious anemia, 148

– See Haserick, J. R.

Brown, C. H.: Idiopathic steatorrhea, 52

–and Perry, J. H., III: Medical treatment of acute ulcerative colitis, 126

Bunts Institute, Frank E.: Diabetes, 60; proceedings diabetes course, 167, 223; medical and surgical disorders of urinary tract, 246

C

Cancer; use of hormones in, 21

Cardiac arrhythmias; diagnosis and treatment of, 185

Cerebral hemiatrophy; double ventricular shift in case of, 17

Colitis, acute toxic ulcerative; medical treatment of, 126

Collins, E. N., and Russell, P. W.: Fatal magnesium poisoning, 162

–See Michels, A. G.

Convulsions; rheumatic brain disease as cause of, 136

Coughing and unconsciousness, the so-called laryngeal vertigo, 200

Crile, George, Jr., McCullagh, E. P., and Glasser, Otto: Radioactive iodine in treatment of hyperthyroidism, 1

Cutaneous lymphoblastoma; skin imprints in, 86

Cysticercosis; intracranial, 74

D

Dempsey, W. S., Dinsmore, R. S., and Hazard, J. B.: Struma lymphomatosa, 132

Diabetes; modern trends in, 109

Diagnosis and treatment of cardiac arrhythmias, 185

Diagnosis and treatment of macrocytosis, 8

Dinsmore, R. S. See Dempsey, W. S.

Double ventricular shift in case of cerebral hemiatrophy, 17

E

Effler, D. B.: Bronchial adenoma, 12

–Mediastinal tumors, 98

–Solitary lung metastasis, 196

Engel, W. J.: Vesical neck resection for neurogenic bladder, 211

Ernstene, A. C.: Diagnosis and treatment of cardiac arrhythmias, 185

Fatal magnesium poisoning, 162

Fistula, bronchohepatic; amoebic hepatic abscess with, 142

G

Gardner, W. J. See McClure, C. C.

Geist, R. M., Jr., and Hughes, C. R.: Double ventricular shift in case of cerebral hemiatrophy, 17

Glasser, Otto. See Crile, George, Jr.

Glaucoma, 61

Goodall, R. J. See Nosik, W. A.

Granulomas; spinal extradural, 205

H

Haden, R. L. See Bortz, D. W.

Hale, D. E.: Arterial infusion, 216

Hannan, J. R., and Mason, R. L.: Spinal extradural granulomas, 205

Haserick, J. R., and Bortz, D. W.: A new diagnostic test for acute disseminated lupus erythematosus, 188

—Skin imprints in cutaneous lymphoblastoma, 86

Hazard, J. B. See Dempsey, W. S.

Higgins, C. C. See Warden, J. G.

Hormones, sex; use of in cancer, 21

Hughes, C. R. See Geist, R. M.

Hyperthyroidism; use of radioactive iodine in treatment of, 1

I

Idiopathic steatorrhea, 52

Infusion, arterial 216

Intestinal intubation, 68

Intestinal obstruction, 154

Intracranial cysticercosis, 74

Intracranial stab wounds; transorbital, 118

Intractable pain; prefrontal lobotomy for relief of, 91

J

Jones, T. E. See Michels, A. G.

K

Karnosh, L. J. See Whitman, J. F.

—See Proudfit, J. P.

Kennedy, R. J.: Glaucoma, 61

L

Laryngeal vertigo, so-called; coughing and unconsciousness, 200

Le Fevre, Fay: Thrombophlebitis, 33

Lobotomy, prefrontal; for relief of intractable pain, 91

Lupus erythematosus, acute disseminated; new diagnostic test for, 158

Lymphoblastoma, cutaneous; skin imprints in, 86

Lymphomatosa; struma, 132

M

Macrocytosis; diagnosis and treatment of, 8

Magnesium poisoning; fatal, 162

Mason, R. L. See Hannan, J. R.

McClure, C. C., Jr., and Gardner, W. J.: Transorbital intracranial stab wounds, 118

McCullagh, E. P. See Crile, George, Jr.

—The use of sex hormones in cancer, 21

Mediastinal tumors, 98

Medical treatment of acute toxic ulcerative colitis, 126

Mesenteric cyst with intestinal obstruction, 47

Michels, A. G., and Jones, T. E.: Mesenteric cyst with intestinal obstruction, 47

—Van Ordstrand, H. S., and Collins, E. N.: Amoebic hepatic abscess with bronchohepatic fistula, 142

Miller, T. G.: Intestinal intubation, 68

N

Neurogenic bladder; vesical neck resection for, 211

New diagnostic test for acute disseminated lupus erythematosus, 158

Nosik, W. A., and Goodall, R. J.: Intracranial cysticercosis, 74

P

Pernicious anemia; value of vitamin B_{12} in, 148

Perry, J. H., III. See Brown, C. H.

Prefrontal lobotomy for relief of intractable pain; value and limitations, 91

Proudfit, J. P., and Karnosh, L. J.: Coughing and unconsciousness; the so-called laryngeal vertigo, 200

R

Radioactive iodine in treatment of hyperthyroidism, 1

Reimplantation of ureter into bladder, 38

Rheumatic brain disease as cause of convulsions, 136

Ricketts, H. T.: Modern trends in diabetes, 109

Root, J. C.: Intestinal obstruction, 154

Russell, P. W. See Collins, E. N.

S

Skin imprints in cutaneous lymphoblastoma, 86

Solitary lung metastasis, 196

Spinal extradural granulomas, 205

Steatorrhea; idiopathic, 52

Struma lymphomatosa, 132

T

Thrombophlebitis, 33

Thrombopenic purpura, 81

Transorbital intracranial stab wounds, 118

Tumors; mediastinal, 98

U

Ulcerative colitis, acute; medical treatment of, 126

Ureter, reimplantation of; into bladder, 38

V

Van Ordstrand, H. S. See Michels, A. G.

Vesical neck resection for neurogenic bladder, 211

Vitamin B_{12}, value of; in pernicious anemia, 148

W

Warden, J. G., and Higgins, C. C.: Reimplantation of ureter into bladder, 38

Whitman, J. F., and Karnosh, L. J.: Rheumatic brain disease as cause of convulsions, 136

Williams, G. H., Jr.: Prefrontal lobotomy for relief of intractable pain, 91